

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 21 June 2001 (21.06.01)	Applicant's or agent's file reference LEA33914-WO
International application No. PCT/EP00/08890	Priority date (day/month/year) 24 September 1999 (24.09.99)
International filing date (day/month/year) 12 September 2000 (12.09.00)	
Applicant FAHRIG, Thomas et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
23 March 2001 (23.03.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LEA33914-WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/08890	International filing date (day/month/year) 12/09/2000	Priority date (day/month/year) 24/09/1999	
International Patent Classification (IPC) or national classification and IPC A61K31/00			
Applicant BAYER AKTIENGESELLSCHAFT			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none">I <input checked="" type="checkbox"/> Basis of the reportII <input type="checkbox"/> PriorityIII <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicabilityIV <input type="checkbox"/> Lack of unity of inventionV <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statementVI <input checked="" type="checkbox"/> Certain documents citedVII <input type="checkbox"/> Certain defects in the international applicationVIII <input type="checkbox"/> Certain observations on the international application			
Date of submission of the demand 23/03/2001		Date of completion of this report 04.01.2002	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Villa Riva, A Telephone No. +49 89 2399 8404 	

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/08890

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-100 as originally filed

Claims, No.:

1-8 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/08890

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1 .

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims 3-8

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/08890

	No:	Claims	2
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2-8
Industrial applicability (IA)	Yes:	Claims	2-8
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

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Section III

1. Present claim 1 relates to the use of an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for the use of only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible. Consequently, the search has been carried out for claims 2-8 only, and the examination will be restricted to those claims.

Section V

2. Reference is made to the following documents:

D1: WO-A-9961413

D2: WO-A-9743239

D3: WO-A-9615096

D4: Trends In Neurosciences (02-1998), 21(2), 75-80

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

3. The subject-matter of present claim 2 does not appear to be novel over D2 (Art. 33(1) and (2) PCT). In this prior art item, inhibitors of MMP are disclosed, which fall within the formula (I').

Among several diseases which are treated by using MMP inhibitors, also multiple sclerosis is mentioned.

4. Even for the novel compounds, the presence of an inventive step does not appear to be acknowledgeable (Art. 33(1) and (3) PCT). D2 and D3 discloses a very high number of compounds with the same biarylbutanoic or biarylpentanoic acid structure and several sorts of substituents to be mmp inhibitors. The problem is therefore, to provide alternative biarylbutanoic or biarylpentanoic acid derivatives as MMP inhibitors. The choice of the present substituents does not appear to be associated with any inventive activity, but rather arbitrary, unless a surprising effect can be

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/08890

shown.

The use of single enantiomers cannot be considered inventive either, because it is a common practice in pharmacology. Also the fact that the two enantiomers possess different activity/selectivity does not appear to be surprising. As far as the usefulness of MMP inhibitors for the treatment of multiple sclerosis is concerned, it is documented in prior art by e.g. D4.

Therefore, since biarylbutanoic or biarylpentanoic acid derivatives with a very similar chemical structure are known as MMP inhibitors, it would be obvious to try them in the treatment of multiple sclerosis. The presence of an inventive step cannot be acknowledged for claims 2-8.

Section VI

The potentially relevant intermediate document WO-A-9961413 (filing date 25.5.99, priority date 27.5.98, publication date 2.12.99) is quoted according to Rules 70.10 and 64.3 PCT.

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PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LEA33914-WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/ EP 00/ 08890	International filing date (day/month/year) 12/09/2000	(Earliest) Priority Date (day/month/year) 24/09/1999
Applicant BAYER AKTIENGESELLSCHAFT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/08890**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1

Present claim 1 relates to the use of an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for the use of only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the use of the compounds according to formula (I') (claim 2) and the compounds listed in claims 4 and 5, their preparation, compositions and therapeutic use.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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INTERNATIONAL SEARCH REPORT

International Application No

EP 00/08890

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/4035 A61K31/53 C07D209/48 C07D253/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X ✓	WO 99 61413 A (BAYER AG) 2 December 1999 (1999-12-02) page 2, line 34 - line 38 examples 15,16 ---	2
X ✓	WO 97 43239 A (BAYER CORPORATION, USA; VAN ZANDT, MICHAEL C.; BRITTELLI, DAVID R.; DIX) 20 November 1997 (1997-11-20) page 11, line 7,8 cpd XIX ---	2
Y	---	3-8
Y ✓	WO 96 15096 A (SCHNEIDER STEPHAN ; BENZ GUENTER H H H (DE); DIXON BRIAN RICHARD (U) 23 May 1996 (1996-05-23) examples 262,267-269,360,419 ---	2-8

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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

22 February 2001

Date of mailing of the international search report

19.04.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Villa Riva, A

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08890

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>YONG VOON WEE ET AL: "Matrix metalloproteinases and diseases of the CNS." TRENDS IN NEUROSCIENCES, vol. 21, no. 2, February 1998 (1998-02), pages 75-80, XP002161136 ISSN: 0166-2236 abstract</p> <p>-----</p>	2-8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP 00/08890

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9961413	A	02-12-1999	AU	4201799 A	13-12-1999
WO 9743239	A	20-11-1997	AU	714207 B	23-12-1999
			AU	3122097 A	05-12-1997
			BR	9709086 A	03-08-1999
			CA	2254731 A	20-11-1997
			CN	1225621 A	11-08-1999
			EP	0923530 A	23-06-1999
			HR	970244 A	30-04-1998
			JP	11510821 T	21-09-1999
WO 9615096	A	23-05-1996	AU	702317 B	18-02-1999
			AU	4197596 A	06-06-1996
			BG	62805 B	31-08-2000
			BG	101482 A	30-01-1998
			BR	9509686 A	30-09-1997
			CA	2201863 A	23-05-1996
			CZ	9701477 A	18-02-1998
			EP	0790974 A	27-08-1997
			FI	972062 A	14-07-1997
			HR	950558 A	31-12-1997
			HU	78083 A	30-08-1999
			JP	10509146 T	08-09-1998
			NO	972220 A	14-07-1997
			PL	320285 A	15-09-1997
			SK	51197 A	05-11-1997
			TR	960422 A	21-06-1996
			US	6166082 A	26-12-2000
			US	5789434 A	04-08-1998
			US	5874473 A	23-02-1999
			US	5886024 A	23-03-1999
			US	5854277 A	29-12-1998
			US	5861427 A	19-01-1999
			US	5861428 A	19-01-1999
			US	5886043 A	23-03-1999
			US	5859047 A	12-01-1999

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(19) World Intellectual Property Organization
International Bureau



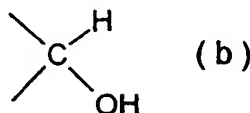
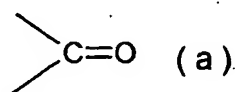
(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/22951 A2

- (51) International Patent Classification⁷: A61K 31/00 (74) Common Representative: BAYER AKTIENGESSELLSCHAFT; 51368 Leverkusen (DE).
- (21) International Application Number: PCT/EP00/08890
- (22) International Filing Date:
12 September 2000 (12.09.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9922710.0 24 September 1999 (24.09.1999) GB
- (71) Applicant (for all designated States except US): BAYER AKTIENGESSELLSCHAFT [DE/DE]; 51368 Leverkusen (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): FAHRIG, Thomas [DE/DE]; Im Luchsfeld 15, 51429 Bergisch Gladbach (DE). HANING, Helmut [DE/DE]; Claudiusweg 3, 42115 Wuppertal (DE). RIEDL, Bernd [DE/DE]; Von-der-Goltz-Strasse 7, 42329 Wuppertal (DE). BRÄUNLICH, Gabriele [DE/DE]; Claudiusweg 9, 42115 Wuppertal (DE). HENNING, Rolf [DE/DE]; Am Jagdhaus 115, 42113 Wuppertal (DE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF SUBSTITUTED 4-BIARYLBUTYRIC AND 5-BIARYLPENTANOIC ACID DERIVATIVES FOR THE TREATMENT OF MULTIPLE SCLEROSIS



(57) Abstract: Use of substituted 4-Biarylbutyric and 5-Biarylpentanoic Acid Derivatives for the Prevention and Treatment of Multiple Sclerosis, pharmaceutical compositions containing them, and a process for using them. The compounds of the invention have the generalized formula (T)_xA-B-D-E-CO₂H wherein A is an aryl or heteroaryl rings; B is an aryl or heteroaryl ring or a bond; each T is a substituent group; x is 0, 1, or 2; the group D represents Formulae (a) or (b), the group E represents a two or three carbon chain bearing one to three substituent groups which are independent or are involved in ring formation, possible structures being shown in the text and claims; and each of the substituents on E is an independent substituent; and include pharmaceutically acceptable salts thereof.

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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 April 2001 (05.04.2001)

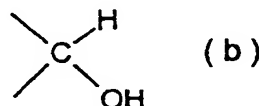
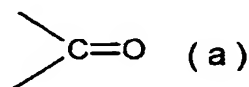
PCT

(10) International Publication Number
WO 01/22951 A2

Not. 50

- (51) International Patent Classification⁷: A61K 31/00 (74) Common Representative: BAYER AKTIENGESSELLSCHAFT; 51368 Leverkusen (DE).
- (21) International Application Number: PCT/EP00/08890
- (22) International Filing Date:
12 September 2000 (12.09.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
9922710.0 24 September 1999 (24.09.1999) GB
- (71) Applicant (for all designated States except US): BAYER AKTIENGESSELLSCHAFT [DE/DE]; 51368 Leverkusen (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): FAHRIG, Thomas [DE/DE]; Im Luchsfeld 15, 51429 Bergisch Gladbach (DE). HANING, Helmut [DE/DE]; Claudiusweg 3, 42115 Wuppertal (DE). RIEDL, Bernd [DE/DE]; Von-der-Goltz-Strasse 7, 42329 Wuppertal (DE). BRÄUNLICH, Gabriele [DE/DE]; Claudiusweg 9, 42115 Wuppertal (DE). HENNING, Rolf [DE/DE]; Am Jagdhaus 115, 42113 Wuppertal (DE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF SUBSTITUTED 4-BIARYLBUTYRIC AND 5-BIARYLPENTANOIC ACID DERIVATIVES FOR THE TREATMENT OF MULTIPLE SCLEROSIS



(57) Abstract: Use of substituted 4-Biarylbutyric and 5-Biarylpentanoic Acid Derivatives for the Prevention and Treatment of Multiple Sclerosis, pharmaceutical compositions containing them, and a process for using them. The compounds of the invention have the generalized formula (T)xA-B-D-E-CO₂H wherein A is an aryl or heteroaryl rings; B is an aryl or heteroaryl ring or a bond; each T is a substituent group; x is 0, 1, or 2; the group D represents Formulae (a) or (b), the group E represents a two or three carbon chain bearing one to three substituent groups which are independent or are involved in ring formation, possible structures being shown in the text and claims; and each of the substituents on E is an independent substituent; and include pharmaceutically acceptable salts thereof.

WO 01/22951 A2

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Use of Substituted 4-Biarylbutyric and 5-Biarylpentanoic Acid Derivatives for the Treatment of Multiple Sclerosis

Field

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This invention relates to the use of enzyme inhibitors, and more particularly, to new and known matrix metalloprotease-inhibiting 4-Biarylbutyric Acids and 5-Biaryl-penta-noic Acids and derivatives thereof, for the prevention and treatment of Multiple Sclerosis.

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Background

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Multiple Sclerosis (MS) is a severely disabling disease which is characterized by focal inflammatory brain lesions. The major site of immunological attack is the myelin sheath formed by oligodendrocytes. As a consequence myelin, which is essential for fast conduction of nerve cell signals, is destroyed and oligodendrocytes eventually die.

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Current therapies (β IFNs, Copaxone) and those currently in clinical development focus on modulation or suppression of the inflammatory processes involved. However, there is still a high medical need for more convenient and, in particular, more efficacious treatments.

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Matrix metalloproteinases (MMPs) are a large family of Zn^{2+} endopeptidases that include 72 kDa (MMP-2) and 92 kDa gelatinase (MMP-9), collagenases (MMP-1, MMP-8, MMP-13), stromelysins 1-3 (MMP-3, MMP-10, MMP-11), matrilysin (MMP-7), macrophage metalloelastase (MMP-12) and membrane-bound MMPs 1-4. They are expressed in inflammatory conditions and are collectively capable of degrading most connective tissue macromolecules.

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Substituted 4-Biarylbutyric and 5-Biarylpentanoic Acid Derivatives as Matrix Metalloprotease Inhibitors are described in WO 96/15096, WO 97/43237, WO 97/43238, WO 97/43239, WO 97/43240, WO 97/43245, WO97/43247 and WO 98/22436.

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Hydroxamic acid derivatives with non-selective MMP-inhibitory activities were shown to be therapeutically efficacious in different animal models of Multiple Sclerosis (*J. Neuroimmunol.* 1997, 74, 85-94; *Ann. Neurol.* 1998, 44, 35-46).

10

Summary

This invention relates to the use for the prevention and treatment of Multiple Sclerosis of compounds having matrix metalloprotease inhibitory activity of the generalized formula (I) :

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In the above generalized formula (I), $(T)_x A$ represents a substituted or unsubstituted aromatic 6-membered ring or heteroaromatic 5 - 6 membered ring containing 1 - 2 atoms of N, O, or S. T represents one or more substituent groups, the subscript x represents the number of such substituent groups, and A represents the aromatic or heteroaromatic ring, designated as the A ring or A unit. When N is employed in conjunction with either S or O in the A ring, these heteroatoms are separated by at least one carbon atom.

25

The substituent group(s) T are independently selected from the group consisting of halogen; alkyl; haloalkyl; haloalkoxy; alkenyl; alkynyl; $-(CH_2)_p Q$ in which p is 0 or an integer of 1 - 4; -alkenyl-Q in which the alkenyl moiety comprises 2 - 4 carbons; and alkynyl-Q in which the alkynyl moiety comprises 2 - 7 carbons. Q in the latter three groups is selected from the group consisting of aryl, heteroaryl, -CN, -CHO,

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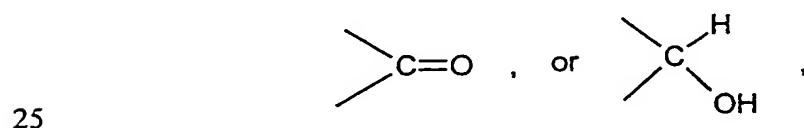
-NO₂, -CO₂R², -OCOR², -SOR³, -SO₂R³, -CON(R⁴)₂, -SO₂N(R⁴)₂, -COR²,
-N(R⁴)₂, -N(R²)COR², -N(R²)CO₂R³, -N(R²)CON(R⁴)₂, -CHN₄, -OR⁴, and -SR⁴.

In these formulae R² represents H, alkyl, aryl, heteroaryl, arylalkyl, or heteroaryl-alkyl. R³ represents alkyl, aryl, heteroaryl, arylalkyl, or heteroaryl-alkyl. R⁴ represents H; alkyl; aryl; heteroaryl; arylalkyl; heteroaryl-alkyl; alkenyl; alkynyl; alkyleneoxy, polyalkyleneoxy, alkyleneethio or alkyleneamino terminated with H, alkyl, or phenyl; haloalkyl; lower alkoxycarbonyl; or acyl. When two R⁴ groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, such as, for example, a morpholine, thiomorpholine, pyrrolidine, or piperidine ring.

Unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom. The A ring may be unsubstituted or may carry up to 2 substituents T. Accordingly, the subscript x is 0, 1, or 2.

In the generalized formula (I), B represents a bond or an optionally substituted aromatic 6-membered ring or a heteroaromatic 5 - 6 membered ring containing 1 - 2 atoms of N, O, or S. When B is a ring, it is referred to as the B ring or B unit. When N is employed in conjunction with either S or O in the B ring, these heteroatoms are separated by at least one carbon atom. There may be 0 - 2 substituents T on ring B.

In the generalized formula (I), D represents



in which R² is defined as above and each R² may be the same or different.

In the generalized formula (I), E represents a chain of n carbon atoms bearing m substituents R⁶, in which the R⁶ groups are independent substituents, or constitute

spiro or nonspiro rings. Rings may be formed in two ways: a) two groups R^6 are joined, and taken together with the chain atom(s) to which the two R^6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R^6 is joined to the chain on which this one group R^6 resides, and taken together with the chain atom(s) to which the R^6 group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring. The number n of carbon atoms in the chain is 2 to 4, and the number m of R^6 substituents is an integer of 1 - 3.

- 10 Each group R^6 is independently selected from the group consisting of:
- *fluorine;
 - *hydroxyl, with the proviso that a single carbon atom may bear no more than one hydroxyl group;
 - *alkyl;
 - 15 *aryl;
 - *heteroaryl;
 - *arylalkyl;
 - *heteroaryl-alkyl;
 - *alkenyl;
 - 20 *aryl-substituted alkenyl;
 - *heteraryl-substituted alkenyl;
 - *alkynyl;
 - *aryl-substituted alkynyl;
 - *heteroaryl-substituted alkynyl;
 - 25 *-(CH₂)_tR⁷, wherein t is 0 or an integer of 1 - 5 and
R⁷ is selected from the group consisting of:
- *N-phthalimidoyl;
 - *N-(1,2-naphthalenedicarboximidoyl);
 - *N-(2,3-naphthalenedicarboximidoyl);
 - 30 *N-(1,8-naphthalenedicarboximidoyl);
 - *N-indoloyl;

*N-(2-pyrrolodinonyl);

*N-succinimidoyl;

*N-maleimidoyl;

*3-hydantoinyl;

5 *1,2,4-urazolyl;

*amido;

*urethane;

*urea;

10 *nonaromatic substituted or unsubstituted heterocycles containing and connected through a N atom, and comprising one or two additional N, O, S, SO, or SO₂, and containing zero, one or two carbonyls, and optionally bearing a fused benzene or pyridine ring;

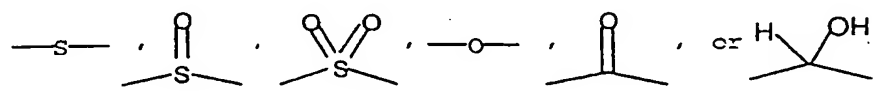
*amino;

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*corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R⁷ group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

20 *-(CH₂)_vZR⁸ in which v is 0 or an integer of 1 - 4, wherein

Z represents



and

R⁸ is selected from the group consisting of:

25

*alkyl;

*aryl;

*heteroaryl;

*arylalkyl;

*heteroaryl-alkyl; and

*-C(O)R⁹ in which R⁹ represents alkyl of at least two carbons, aryl, heteroaryl, arylalkyl, or heteroaryl-alkyl;

and with the further provisos that

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- when R⁸ is -C(O)R⁹, Z is S or O;
- when Z is O, R⁸ may also be alkyleneoxy or polyalkyleneoxy terminated with H, alkyl, or phenyl; and

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*trialkylsilyl-substituted alkyl.

Furthermore, aryl or heteroaryl portions of any of the T or R⁶ groups optionally may bear up to two substituents selected from the group consisting of
15 -(CH₂)_yC(R⁴)(R³)OH, -(CH₂)_yOR⁴, -(CH₂)_ySR⁴, -(CH₂)_yS(O)R⁴,
-(CH₂)_yS(O)₂R⁴, -(CH₂)_ySO₂N(R⁴)₂, -(CH₂)_yN(R⁴)₂, -(CH₂)_yN(R⁴)COR¹²,
-OC(R⁴)₂O- in which both oxygen atoms are connected to the aryl ring,
(CH₂)_yCOR⁴, -(CH₂)_yCON(R⁴)₂, -(CH₂)_yCO₂R⁴, -(CH₂)_yOCOR⁴, -halogen,
-CHO, -CF₃, -NO₂, -CN, and -R³, in which y is 0 - 4. R³ and R⁴ are defined as
20 above; in addition, any two R⁴ which are attached to one nitrogen may be joined to
form a heterocycle such as morpholine, thiomorpholine, pyrrolidine, or a piperidine ring.

Pharmaceutically acceptable salts of these compounds as well as commonly used
25 prodrugs of these compounds such as O-acyl derivatives of invention compounds
which contain hydroxy groups are also within the scope of the invention.

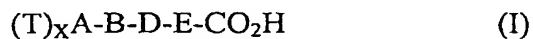
In addition to the above-described compounds, the invention also relates to pharma-
ceutical compositions having matrix metalloprotease inhibitory activity, which
compositions comprise a compound of the invention as described above and in more
30 detail in the detailed description below, and a pharmaceutically acceptable carrier.

The invention also relates to a method of treating a mammal such as a human, a farm animal, or a domestic pet, to achieve an effect, in which the effect is treatment and prevention of Multiple Sclerosis.

5 Detailed Description

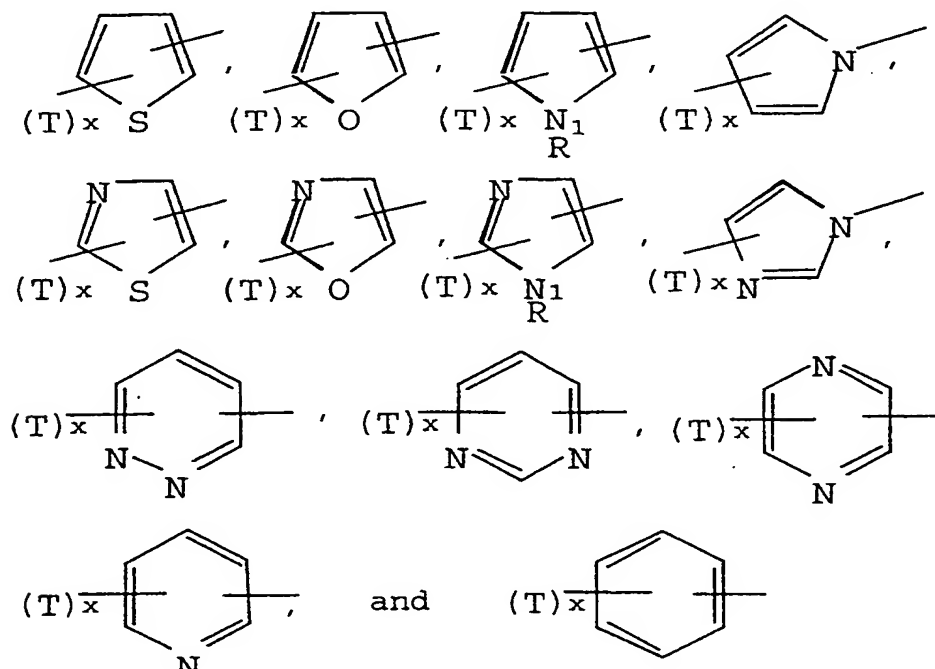
Surprisingly it has been found that particularly useful for the use for the prevention and treatment of Multiple Sclerosis are compounds having matrix metalloprotease inhibitory activity of the generalized formula:

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in which $(T)_x A$ represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:

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in which R^1 represents H or alkyl of 1 - 3 carbons.

In these structures, the aromatic ring is referred to as the A ring or A unit, and each T represents a substituent group, referred to as a T group or T unit. Substituent groups T are independently selected from the group consisting of: the halogens -F, -Cl, -Br, and -I; alkyl of 1 - 10 carbons; haloalkyl of 1 - 10 carbons; haloalkoxy of 1 - 10 carbons; alkenyl of 2 - 10 carbons; alkynyl of 2 - 10 carbons; $-(CH_2)_pQ$ in which p is 0 or an integer 1 - 4; -alkenyl-Q in which the alkenyl moiety comprises 2 - 4 carbons; and -alkynyl-Q in which the alkenyl moiety comprises 2 - 7 carbons. Q in each of the latter three groups is selected from the group consisting of aryl of 6 - 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; -CN; -CHO; -NO₂; -CO₂R²; -OCOR²; -SOR³; -SO₂R³; -CON(R⁴)₂; -SO₂N(R⁴)₂; -C(O)R²; -N(R⁴)₂; -N(R²)COR²; -N(R²)CO₂R³; -N(R²)CON(R⁴)₂; -CHN₄; -OR⁴; and -SR⁴. The groups R², R³, and R⁴ are defined as follows.

R² represents H; alkyl of 1 - 6 carbons; aryl of 6 - 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons.

R³ represents alkyl of 1 - 4 carbons; aryl of 6 - 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons.

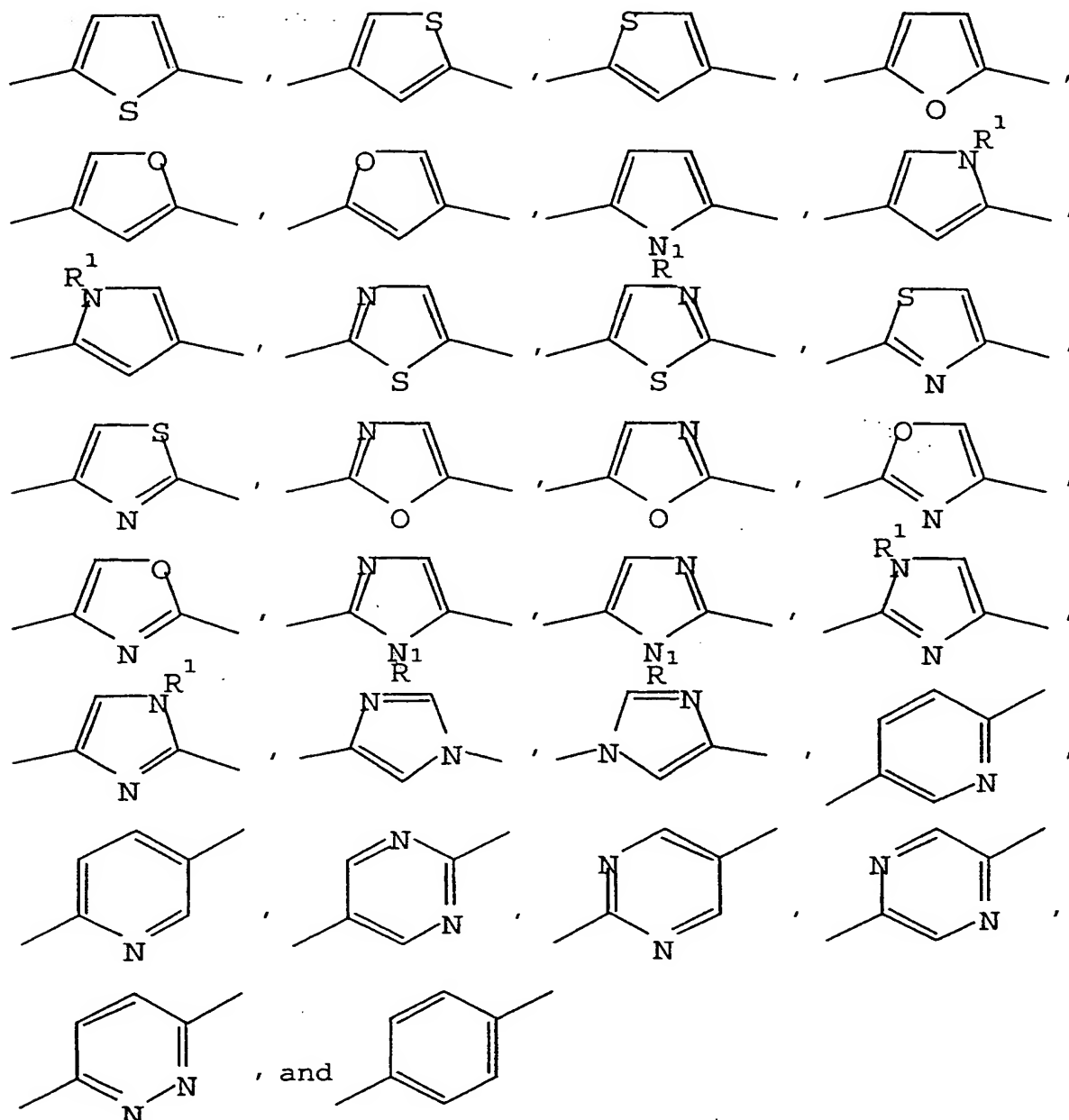
R⁴ represents H; alkyl of 1 - 12 carbons; aryl of 6 - 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9

carbons and at least one N, O, or S heteroatom and the alkyl portion contains
1 - 4 carbons; alkenyl of 2 - 12 carbons; alkynyl of 2 - 12 carbons;
- $(C_qH_{2q}O)_rR^5$ in which q is 1-3, r is 1 - 3, and R^5 is H provided q is greater
5 than 1, or R^5 is alkyl of 1 - 4 carbons, or phenyl; alkylenethio terminated with
H, alkyl of 1-4 carbons, or phenyl; alkyleneamino terminated with H, alkyl of
1-4 carbons, or phenyl; $-(CH_2)_sX$ in which s is 1-3 and X is halogen;
-C(O)OR²; or -C(O)R².

10 When two R^4 groups are situated on a nitrogen, they may be joined by a bond to
form a heterocycle, such as, for example, a morpholine, thiomorpholine, pyrrolidine,
or piperidine ring.

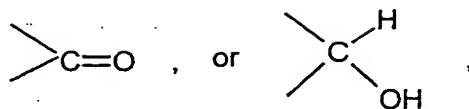
15 Any unsaturation in a moiety which is attached to Q or which is part of Q is sepa-
rated from any N, O, or S of Q by at least one carbon atom, and the number of sub-
stituents, designated x, is 0, 1, or 2.

In the generalized formula (I), B represents a bond or an optionally substituted
aromatic or heteroaromatic ring selected from the group consisting of:



in which R^1 is defined as above and each R^1 may be the same or different. These rings are referred to as the B ring or B unit. There may be 0-2 substituents T on the B ring, T being defined as above.

In the generalized formula (I), D represents the moieties

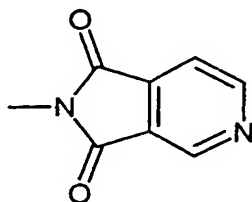


In the generalized formula (I), E represents a chain of n carbon atoms bearing m substituents R⁶, referred to as R⁶ groups or R⁶ units. The R⁶ groups are independent substituents, or constitute spiro or nonspiro rings. Rings may be formed in two ways: a) two groups R⁶ are joined, and taken together with the chain atom(s) to which the two R⁶ group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R⁶ is joined to the chain on which this one group R⁶ resides, and taken together with the chain atom(s) to which the R⁶ group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring. The number n of carbon atoms in the chain is 2 or 3, and the number m of R⁶ substituents is an integer of 1 - 3.

Each group R⁶ is independently selected from the group consisting of the substituents listed below as items 1) - 16).

- 1) fluorine;
- 2) hydroxyl, with the proviso that a single carbon atom may bear no more than one hydroxyl group;
- 3) alkyl of 1 - 10 carbons;
- 4) aryl of 6 - 10 carbons;
- 5) heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
- 6) arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

- 7) heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;
- 5 8) alkenyl of 2 - 10 carbons;
- 9) aryl-alkenyl in which the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;
- 10 10) heteroaryl-alkenyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 - 5 carbons;
- 11) alkynyl of 2 - 10 carbons;
- 15 12) aryl-alkynyl in which the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;
- 13) heteroaryl-alkynyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;
- 20 14) $-(CH_2)_tR^7$ in which t is 0 or an integer of 1 - 5 and R^7 is selected from the group consisting of
- 25



as well as corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R^7 group comprises 4 - 9 carbons and at least one N, O, or S heteroatom. In such R^7 groups, Y represents O or S; R^1 , R^2 , and R^3 are as defined above, and each R^1 , R^2 and R^3 may be the same or different; and u is 0, 1, or 2;

- 15) $-(CH_2)_vZR^8$ in which v is 0 or an integer of 1 to 4; Z represents -S-, -S(O)-, -SO₂-, -O-, carbonyl, or -CH(OH)-; and R^8 is selected from the group consisting of: alkyl of 1 to 12 carbons; aryl of 6 to 10 carbons; heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; arylalkyl in which the aryl portion contains 6 to 10 carbons and the alkyl portion contains 1 to 4 carbons; heteroaryl-alkyl in which the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons; -C(O) R^9 in which R^9 represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons, with the provisos that
- when R^8 is -C(O) R^9 , Z is -S- or -O-;
 - when Z is -O-, R^8 may also be $-(C_qH_{2q}O)_rR^5$ in which q, r, and R^5 are as defined above;
- 16) $-(CH_2)_wSi(R^{10})_3$ in which w is an integer of 1 to 3, and R^{10} represents alkyl of 1 to 4 carbons.

In addition, aryl or heteroaryl portions of any of the T or R^6 groups optionally may bear up to two substituents selected from the group consisting of $-(CH_2)_yC(R^4)(R^3)OH$, $-(CH_2)_yOR^4$, $-(CH_2)_ySR^4$, $-(CH_2)_yS(O)R^4$, $-(CH_2)_yS(O)_2R^4$, $-(CH_2)_ySO_2N(R^4)_2$, $-(CH_2)_yN(R^4)_2$, $-(CH_2)_yN(R^4))COR^3$, $-OC(R^4))_2O-$ in which both oxygen atoms are connected to the aryl ring, $-(CH_2)_yCOR^4$, $-(CH_2)_yCON(R^4)_2$, $-(CH_2)_yCO_2R^4$, $-(CH_2)_yOCOR^4$, -halogen,

-CHO, -CF₃, -NO₂, -CN, and -R³, in which y is 0 - 4; R³ is defined as above; R⁴ is defined as above, and each R³ or R⁴ may be the same or different and in addition, any two R⁴ which are attached to one nitrogen may be joined to form a heterocycle, such as a morpholine, thiomorpholine, pyrrolidine, or piperidine ring.

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Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds such as O-acyl derivatives of these compounds are also within the scope of the invention.

10 In the compounds of the invention, the following are preferred.

The substituent group T, when it is on the ring A, is preferably halogen, 1-alkynyl-Q, or an ether OR⁴ wherein R⁴ is preferably alkyl of 1 - 12 carbons or arylalkyl in which the aryl portion is 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons.

15 Most preferably, T is halogen, or $\text{—C}\equiv\text{C—}(\text{CH}_2)_t\text{OH}$ in which t is an integer of 1 - 5, and when T is OR⁴, R⁴ is alkyl of 1 - 6 carbons, or benzyl.

The subscript x, which defines the number of T substituents, is preferably 1 or 2, most preferably 1, and this substituent T is preferably on the 4- position of ring A.

20

The A ring is preferably a phenyl or thiophene ring, most preferably phenyl. The A ring preferably bears at least one substituent group T, preferably located on the position furthest from the position of the A ring which is connected to the B ring.

25 The B moiety of generalized formula (I) is a bond or a substituted or unsubstituted aromatic or heteroaromatic ring, in which any substituents are groups which do not cause the molecule to fail to fit the active site of the target enzyme, or disrupt the relative conformations of the A and B rings, such that they would be detrimental. Such groups may be, but are not limited to, moieties such as lower alkyl, lower alkoxy, CN, NO₂, halogen, etc. The B moiety is preferably a 1,4-phenylene or 2,5-
30 thiophene ring, most preferably 1,4-phenylene.

5 The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the enantiomers or diastereomers and their respective mixtures. These mixtures of the enantiomers and diastereomers can be separated into the stereoisomerically uniform constituents in a known manner.

10 The D unit is most preferably a carbonyl or a -CHOH- group.

The group R^6 is preferably:

- 15
- 1) arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;
 - 2) $-(CH_2)_tR^7$ wherein t is 0 or an integer of 1 - 5 and R^7 is an imido group fused to an aromatic residue, or the 1,2,3-benzotriazin-4(3H)-one-3-yl group; or
 - 20 3) $-(CH_2)_vZR^8$ wherein v is 0 or an integer of 1 - 4, Z is S or O, and R^8 is aryl of 6 - 10 carbons or arylalkyl wherein the aryl portion contains 6 to 12 carbons and the alkyl portion contains 1 to 4 carbons.

25 The group R^6 is most preferably one of the following, and in these, any aromatic moiety is preferably substituted:

- 1) arylalkyl wherein the aryl portion is phenyl and the alkyl portion contains 1 - 4 carbons;

2) $-(CH_2)_tR^7$ wherein t is an integer of 1 - 3, and R^7 is N-phthalimidoyl, 1,2,3-benzotriazin-4(3H)-one-3-yl, N-(1,2-naphthalenedicarboximidoyl), N-(2,3-naphthalenedicarboximidoyl), or N-(1,8-naphthalenedicarboximidoyl); or

5 3) $-(CH_2)_vZR^8$ wherein v is an integer of 1 - 3, Z is S, and R^8 is phenyl.

It is to be understood that as used herein, the term "alkyl" means straight, branched, cyclic, and polycyclic materials. The term "haloalkyl" means partially or fully halogenated alkyl groups such as $-(CH_2)_2Cl$, $-CF_3$ and $-C_6F_{13}$, for example.

10

In one of its embodiments, the invention relates to compounds of generalized formula (I) in which at least one of the units A, B, T, and R^6 comprises a heteroaromatic ring. Preferred heteroaromatic ring-containing compounds are those in which the heteroaryl groups are heteroaryl of 4 - 9 carbons comprising a 5 - 6
15 membered heteroaromatic ring containing O, S, or NR^1 when the ring is 5-membered, and N when said ring is 6-membered. Particularly preferred heteroaromatic ring-containing compounds are those in which at least one of the A and B units comprises a thiophene ring. When A unit is thiophene, it is preferably connected to B unit at position 2 and carries one substituent group T on position 5.
20 When B Unit is thiophene, it is preferably connected through positions 2 and 5 to D and A units respectively.

In another embodiment, the invention relates to compounds of generalized formula (I), in the E unit of which n is 2 and m is 1. These compounds thus possess two
25 carbon atoms between the D unit and carboxyl group, and carry one substituent on this two-carbon chain.

In another of its embodiments, the invention relates to compounds of generalized formula (I) in which the A ring is a substituted or unsubstituted phenyl group, the B
30 ring is p-phenylene, and aryl portions of any aryl-containing T and R^6 moieties

contain only carbon in the rings. These compounds thus contain no heteroaromatic rings.

5 In another of its embodiments, the invention relates to compounds of generalized formula (I) in which m is 1 and R^6 is an independent substituent. These compounds are materials which contain only a single substituent R^6 on the E unit, and this substituent is not involved in a ring.

10 Preferred compounds of general formula (I) in which R^6 is $-(CH_2)_tR^7$ have t as an integer of 1-5. Preferred compounds of general formula (I) in which R^6 is $-(CH_2)_vZR^8$ have v as an integer of 1-4 and Z as -S- or -O-. Preferred compounds of general formula (I) in which R^6 is alkyl contain 4 or more carbons in said alkyl and those in which R^6 is arylalkyl contain 2-3 carbons in the alkyl portion of said aryl-alkyl.

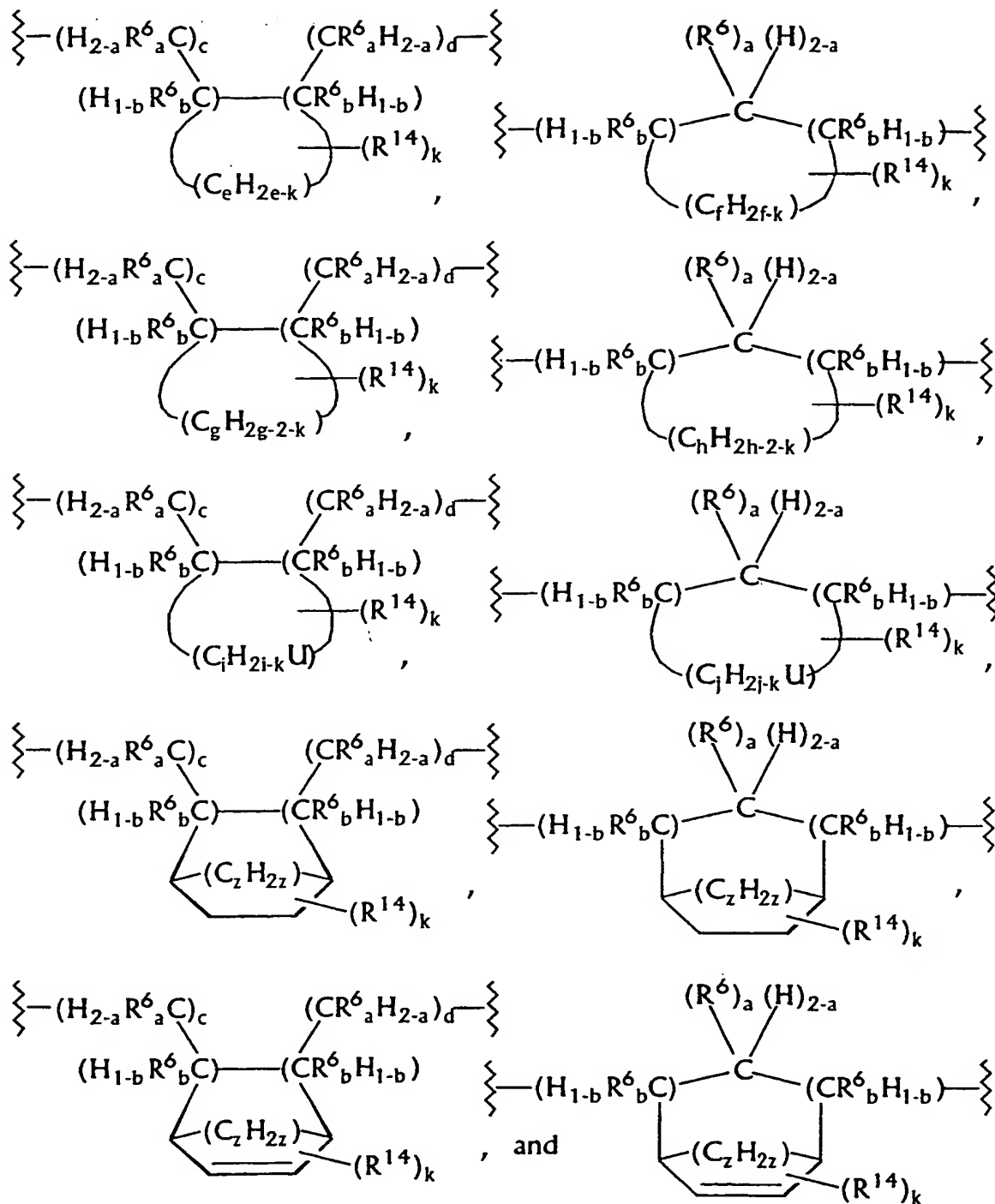
15 In another of its embodiments, the invention relates to compounds of generalized formula (I) in which the number of substituents m on the E unit is 2 or 3; and when m is 2, both groups R^6 are independent substituents, or together constitute a spiro ring, or one group R^6 is an independent substituent and the other constitutes a spiro ring; and when m is 3, two groups R^6 are independent substituents and one group R^6 constitutes a ring, or two groups R^6 constitute a ring and one group R^6 is an independent substituent, or three groups R^6 are independent substituents. This subset therefore contains compounds in which the E unit is di- or trisubstituted, and in the disubstituted case any rings formed by one or both R^6 groups are spiro rings, and in the trisubstituted case, the R^6 groups may form either spiro or nonspiro rings.

20 In another of its embodiments, the invention relates to compounds of generalized formula (I) in which the number of substituents m on the E unit is 1 or 2; and when m is 1, the group R^6 constitutes a nonspiro ring; and when m is 2, both groups R^6 together constitute a nonspiro ring or one group R^6 is an independent substituent and the other constitutes a nonspiro ring. This subset therefore contains compounds in

30

which the E unit carries one or two substituents R^6 , and at least one of these substituents is involved in a nonspiro ring.

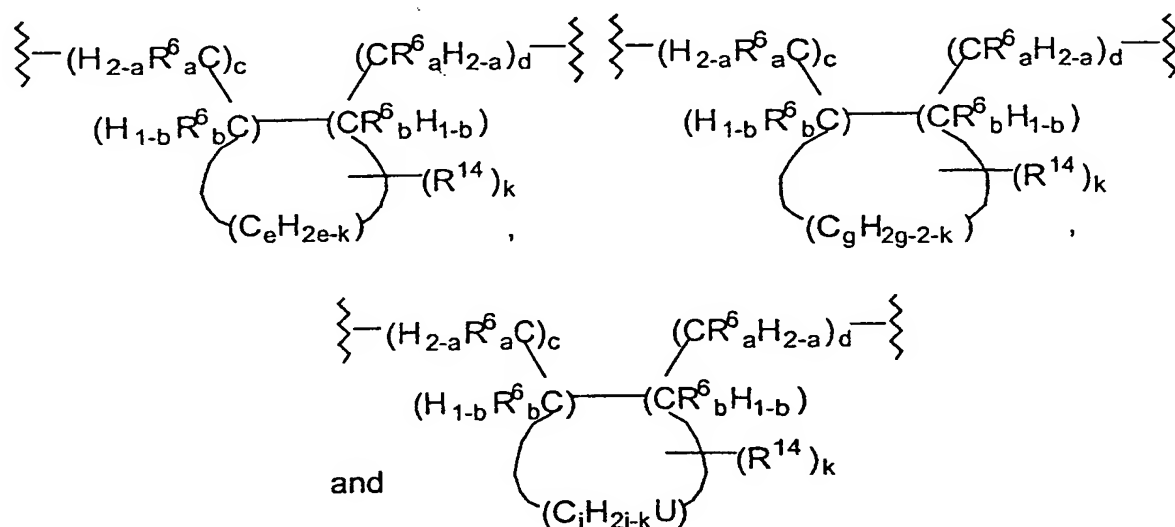
5 More particularly, representative compounds of generalized formula (I) in which one or more of the substituent groups R^6 are involved in formation of nonspiro rings have E units of the following structures:



in which a is 0, 1, or 2; b is 0 or 1; c is 0 or 1; d is 0 or 1; c + d is 0 or 1; e is 1 - 5; f is 1 - 4; g is 3 - 5; h is 2 - 4; i is 0 - 4; j is 0 - 3; k is 0 - 2; the total number of groups R⁶ is 0, 1, or 2; U represents O, S, or NR¹; and z is 1 or 2; Each group R¹⁴ is independently selected from the group consisting of: alkyl of 1 - 9 carbons; arylalkyl

in which the alkyl portion contains 1 - 7 carbons and the aryl portion contains 6 - 10 carbons; alkenyl of 2 - 9 carbons; aryl-substituted alkenyl in which the alkenyl portion contains 2 - 4 carbons and the aryl portion contains 6 - 10 carbons; alkynyl of 2 - 9 carbons; aryl-substituted alkynyl in which the alkynyl portion contains 2 - 4 carbons and the aryl portion contains 6 - 10 carbons; aryl of 6 - 10 carbons; -COR²; -CH(OH)R²; -CO₂R³; -CON(R²)₂; -(CH₂)_tR⁷ in which t is 0 or an integer of 1 - 4; and -(CH₂)_vZR⁸ in which v is 0 or an integer of 1 to 3, and Z represents -S-, S(O), SO₂, or -O-. R¹, R⁷, and R⁸ have been defined above.

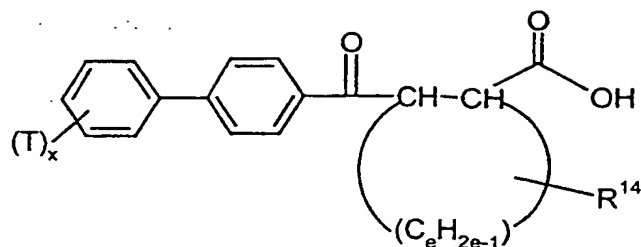
10 Preferred compounds of generalized formula (I) in which one or more of the substituent groups R⁶ are involved in formation of nonspiro rings have E units of the following structures:



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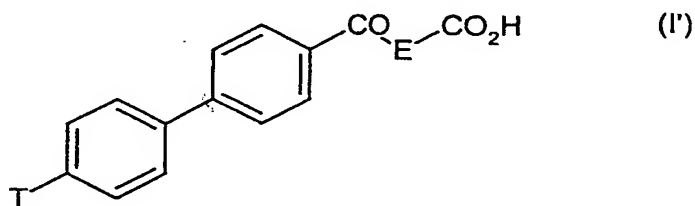
in which a, b, c, d, (c + d), e, g, i, k, the total number of groups R⁶, U, and R¹⁴ are as defined above.

20 The more preferred compounds for the use for the prevention and treatment of Multiple Sclerosis of generalized formula (I), in which one or more of the substituent groups R⁶ are involved in formation of nonspiro rings have the formula



in which the subscript x is 1 or 2; one substituent T is located on the 4-position of the A ring, relative to the point of attachment between the A and B rings; e is 2 or 3; and
 5 R¹⁴ is as defined above.

Very particularly preferred is the use of the compounds of the general formula (I')

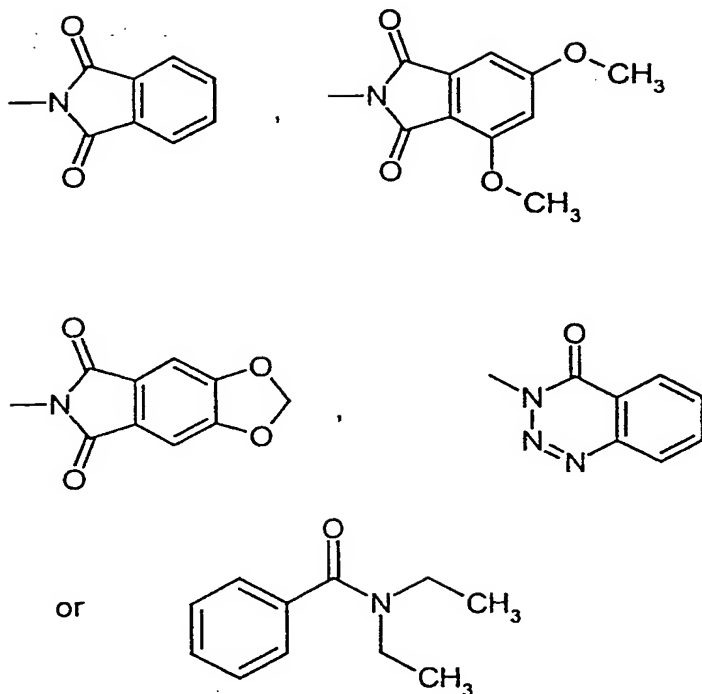


10 wherein

T is (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

15 CO-E-CO₂H represents a 3-carboxyl-5-R⁷-pentan-1-on-1-yl- or a 2-carboxyl-3-(R⁷-methyl)-cyclopentan-1-yl)carbonyl-residue, wherein

R⁷ represents a group of the formula



and their salts.

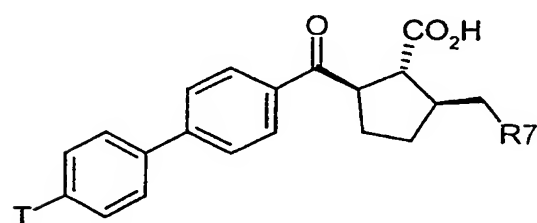
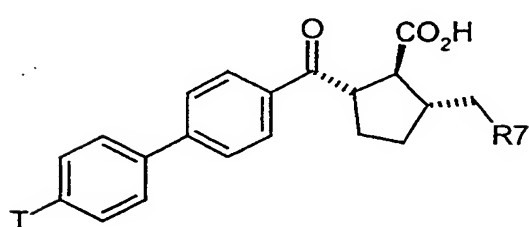
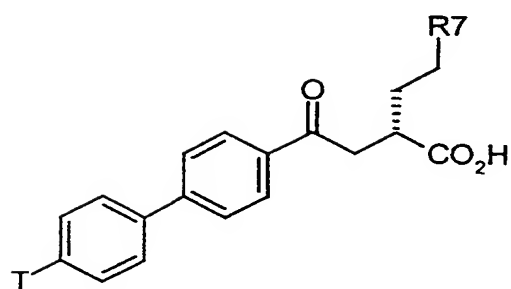
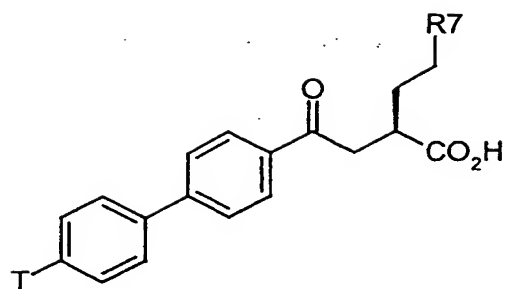
- 5 In case of the cyclopentane derivatives the trans, trans-diastereomers are preferred.

Furthermore preferred is the use of such enantiomers of pairs of enantiomers at a chiral center adjacent to the carboxylic acid moiety of the group of the formula CO-E-CO₂H in compounds of the general formula (I') that more potently inhibit MMP-2 and/or MMP-9.

10

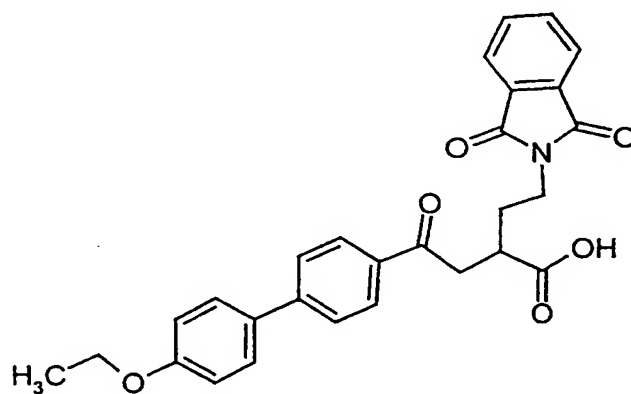
The pairs of enantiomers can be exemplified by the following structures:

- 24 -

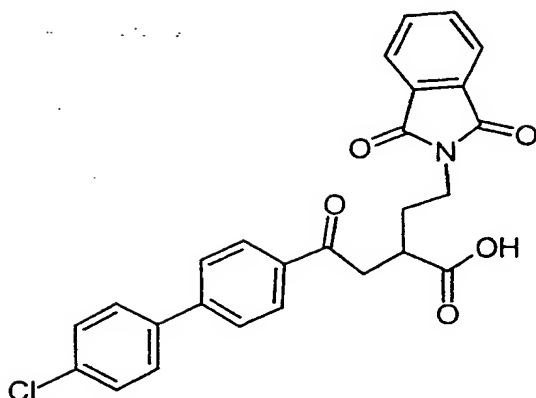


Especially preferred is the use of the following compounds:

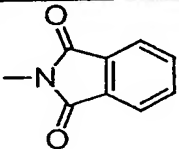
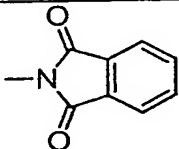
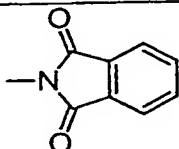
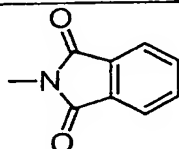
- 5 (+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,

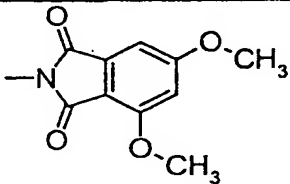
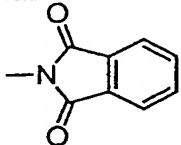
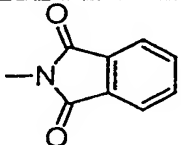
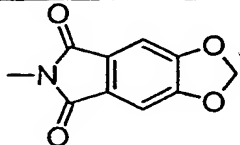
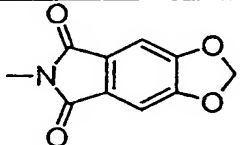
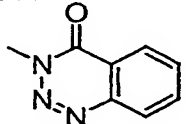
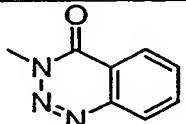


- 10 (+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid



In another aspect of the invention the following new compounds of the general formula (I') are provided, wherein CO-E-CO₂H represents a 3-carboxyl-5-R⁷-pentan-1-on-1-yl-residue, and wherein T and R⁷ have the meaning indicated in the following table:

T	R ⁷	racemate, (+)- or (-)-enantiomer	
OEt		(+)	;
OEt		(-)	;
OAc		rac	;
OH		rac	;

T	R ⁷	racemate, (+)- or (-)-enantiomer	
Cl		rac	;
Br		(+)	;
Br		(-)	;
Cl		(+)	;
Cl		(-)	;
CN		rac	or
OCF ₃		rac	.

General Preparative Methods:

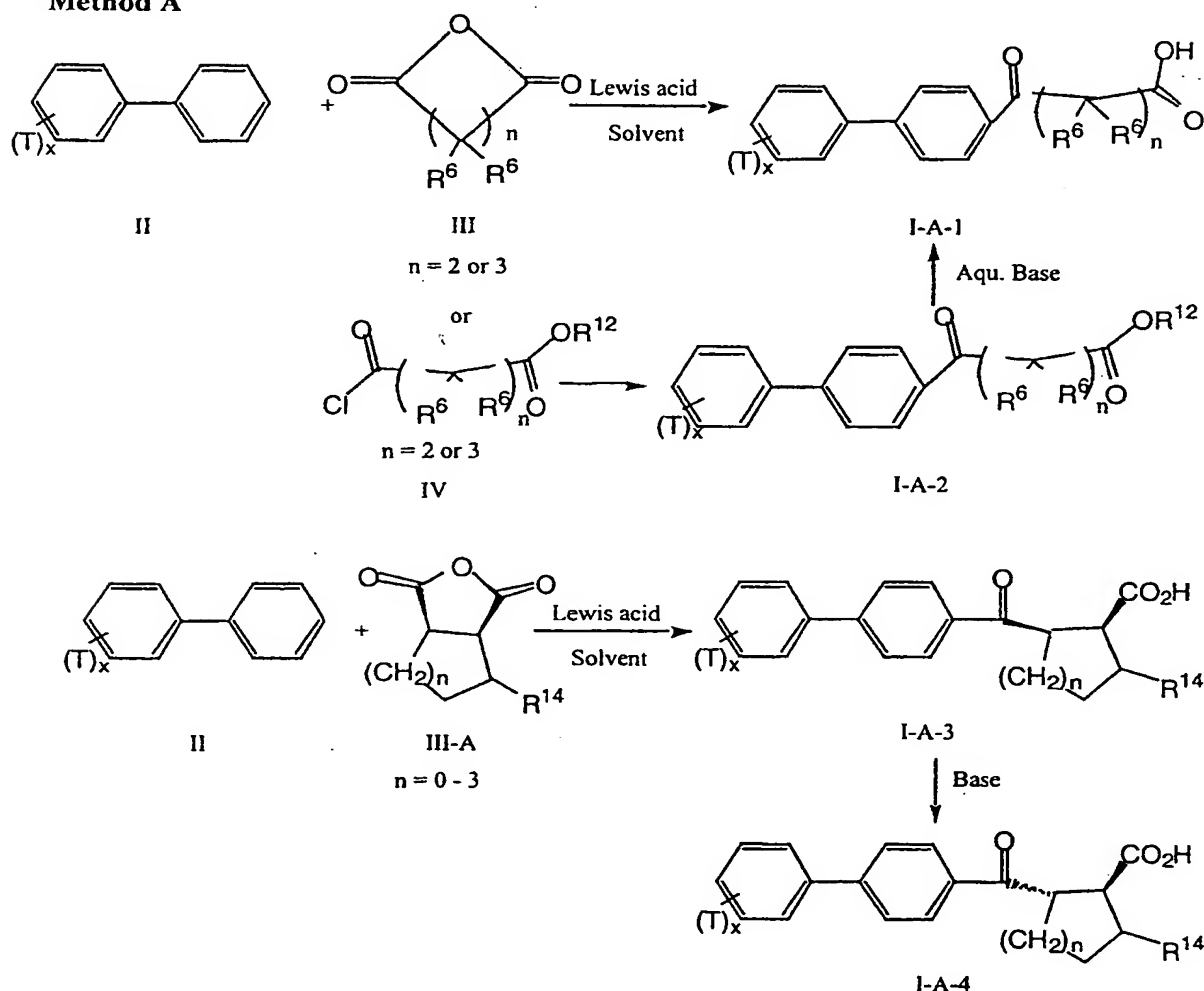
The compounds of the invention may be prepared by use of known chemical reactions and procedures as described in details in WO 96/15096, WO 97/43237, WO 97/43238, WO 97/43239, WO 97/43240, WO 97/43245, WO97/43247 and WO 98/22436. Nevertheless, the following general preparative methods are presented to aid the reader in synthesizing the inhibitors. General methods A through K may be used to prepare appropriately substituted 4-biaryl-4-oxobutanoic acids, 4-aryl-4-oxobutanoic acids, 5-biaryl-5-oxopentanoic acids, or 5-aryl-5-oxopentanoic acids. These general methods are also found in WO 96/15096 along with exemplary preparations of the keto acids. The choice of a specific synthetic method is dictated by the proviso that the conditions used do not effect undesired changes in the T or R⁶ moieties of the compounds prepared.

All variable groups of these methods are as described in the generic description if they are not specifically defined below. The variable subscript n is independently defined for each method. When a variable group with a given symbol (i.e. R⁶ or T) is used more than once in a given structure, it is to be understood that each of these groups may be independently varied within the range of definitions for that symbol. As defined above, the compounds of the invention contain as the E unit a chain of 2 or 3 carbon atoms bearing 1 to 3 substituents R⁶ which are not defined as H. By contrast, it is to be noted that in the general method schemes below, the R⁶ groups are used as if their definition includes H, to show where such R⁶ groups may exist in the structures, and for ease in drawing. No change in the definition of R⁶ is intended by this non-standard usage, however. Thus, only for purposes of the general method schemes below, R⁶ may be H in addition to the moieties set forth in the definition of R⁶. The ultimate compounds contain 1 to 3 non-hydrogen groups R⁶.

General Method A - The key intermediates in which the rings A and B are substituted phenyl and phenylene respectively are conveniently prepared by use of a Friedel-Crafts reaction of a substituted biphenyl II with an activated acyl- containing

intermediate such as the succinic or glutaric anhydride derivative III or acid chloride IV in the presence of a Lewis acid catalyst such as aluminum trichloride in an aprotic solvent such as 1,1,2,2-tetrachloroethane. The well known Friedel-Crafts reaction can be carried out with many alternative solvents and acid catalysts as described by E. Berliner, *Org. React.*, 5, 229 (1949) and H. Heaney, *Comp. Org. Synth.*, 2, 733 (1991).

Method A



10 If the anhydride III is monosubstituted or multiplesubstituted in an unsymmetrical way, the raw product I-A often exists as a mixture of isomers via attack of the anhydride from either of the two carbonyls. The resultant isomers can be separated into

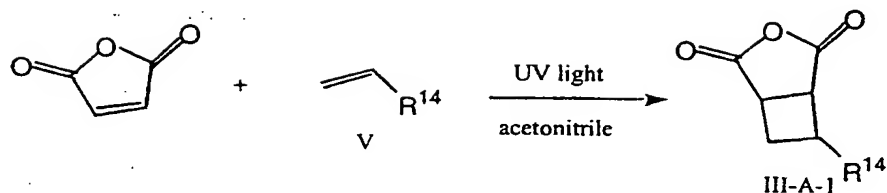
pure forms by crystallization or chromatography using standard methods known to those skilled in the art.

When they are not commercially available, the succinic anhydrides III can be prepared via a Stobbe Condensation of a dialkyl succinate with an aldehyde or ketone (resulting in side chain R^6), followed by catalytic hydrogenation, hydrolysis of a hemiester intermediate to a diacid and then conversion to the anhydride III by reaction with acetyl chloride or acetic anhydride. Alternatively, the hemiester intermediate is converted by treatment with thionyl chloride or oxalyl chloride to the acid chloride IV in which R^{12} is lower alkyl. For a review of the Stobbe condensation, including lists of suitable solvents and bases see W.S. Johnson and G.H. Daub, *Org. React.*, 6, 1 (1951). This method, as applied to the preparation of III ($R^6 = H$, isobutyl and H, n-pentyl), has been described by D. Wolanin, et al., US Patent 4,771,038, Sep. 13, 1988.

Method A is especially useful for the preparation of cyclic key intermediates such as I-A-3 in which two R^6 groups are connected in a methylene chain to form a 4-7 membered ring. Small ring (3-5 member) anhydrides are readily available only as cis isomers which yield cis invention compounds I-A-3. The trans compounds I-A-4 are then prepared by treatment of I-A-3 with a base such as DBU in THF.

The substituted four member ring starting material anhydrides such as III-A-1 are formed in a photochemical 2+2 reaction as shown below. This method is especially useful for the preparation of compounds in which R^{14} is acetoxy or acetoxymethylene. After the subsequent Friedel-Crafts reaction the acetate can be removed by basic hydrolysis and the carboxyl protected by conversion to 2-(trimethylsilyl)ethyl ester. The resultant intermediate with $R^{14} = CH_2OH$ can be converted to key intermediates with other R^{14} groups by using procedures described in General Method K.

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The Friedel Crafts method is also useful when double bonds are found either between C-2 and C-3 of a succinoyl chain (from maleic anhydride or 1-cyclopentene-1,2-dicarboxylic anhydride, for example) or when a double bond is found in a side chain, such as in the use of itaconic anhydride as starting material to yield products in which two R^6 groups as found on one chain carbon together form an exo-methylene ($=\text{CH}_2$) group. Subsequent uses of these compounds are described in Methods D and E.

General Method B - Alternatively key intermediates can be prepared via a reaction sequence involving mono-alkylation of a dialkyl malonate VI with an alkyl halide to form intermediate VII, followed by alkylation with a halomethyl biphenyl ketone VIII to yield intermediate IX. Compounds of structure IX are then hydrolyzed with aqueous base and then heated to decarboxylate the malonic acid intermediate and yield I-B-2 (Method B-1). By using one equivalent of aqueous base the esters I-B-2 with R^{12} as alkyl are obtained, and using more than two equivalents of base the acid compounds ($\text{R}^{12} = \text{H}$) are obtained. Optionally, heat is not used and the diacid or acid-ester I-B-1 is obtained. Alternatively, the diester intermediate IX can be heated with a strong acid such as concentrated hydrochloric acid in acetic acid in a sealed tube at about 110 °C for about 24 hr to yield I-B-2 ($\text{R}^{12} = \text{H}$).

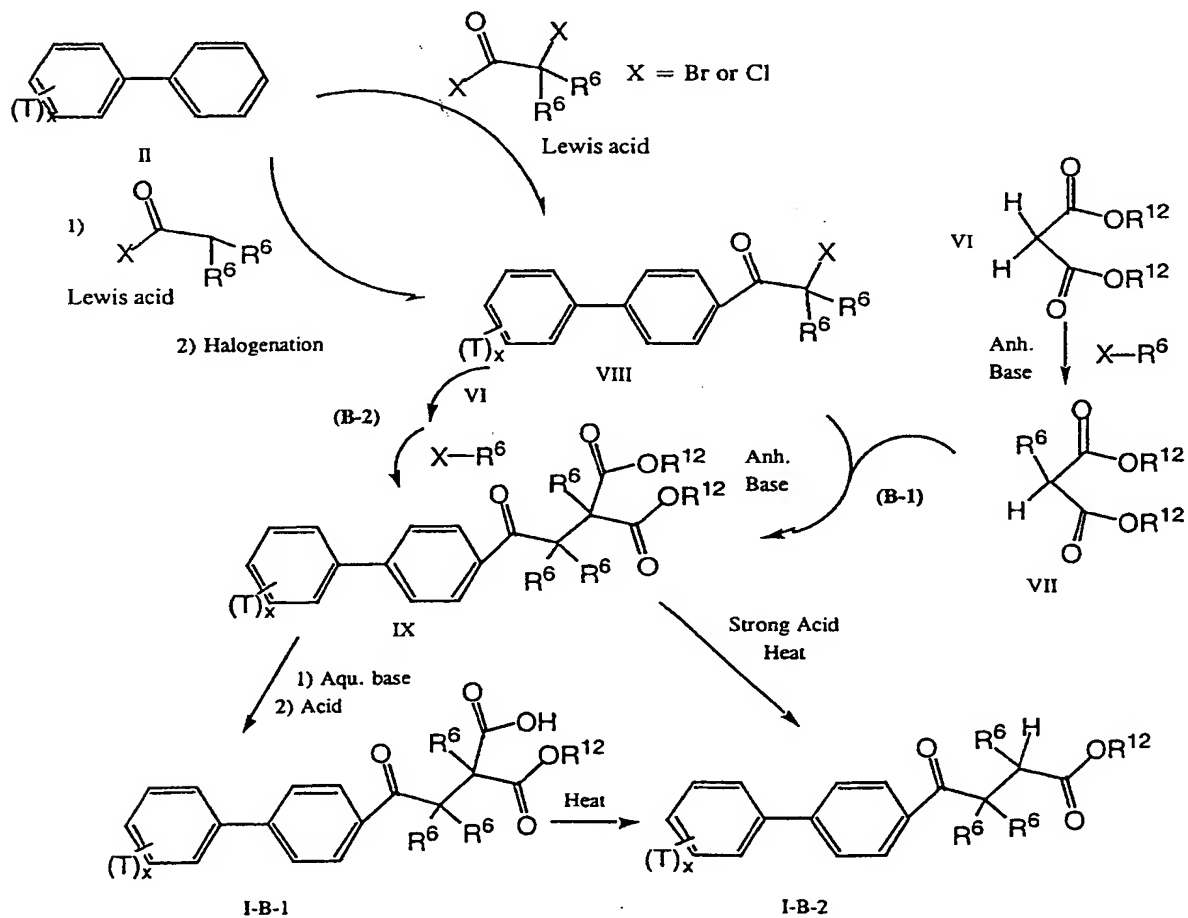
Alternatively, the reaction of VI with VIII can be conducted before that with the alkyl halide to yield the same IX (Method B-2).

Intermediates VIII are formed from biphenyls II in a Friedel-Craft reaction with haloacetyl halides such as bromoacetyl bromide or chloroacetyl chloride. Alternatively, the biphenyl can be reacted with acetyl chloride or acetic anhydride and the

resultant product halogenated with, for example, bromine to yield intermediates VIII (X = Br).

Method B has the advantage of yielding single regio isomers whereas Method A yields mixtures. Method B is especially useful when the side chains R^6 contain aromatic or heteroaromatic rings that may participate in intramolecular acylation reactions to give side products if Method A were to be used. This method is also very useful when the R^6 group adjacent to the carboxyl of the final compound contains heteroatoms such as oxygen, sulfur, or nitrogen, or more complex functions such as imide rings.

Method B



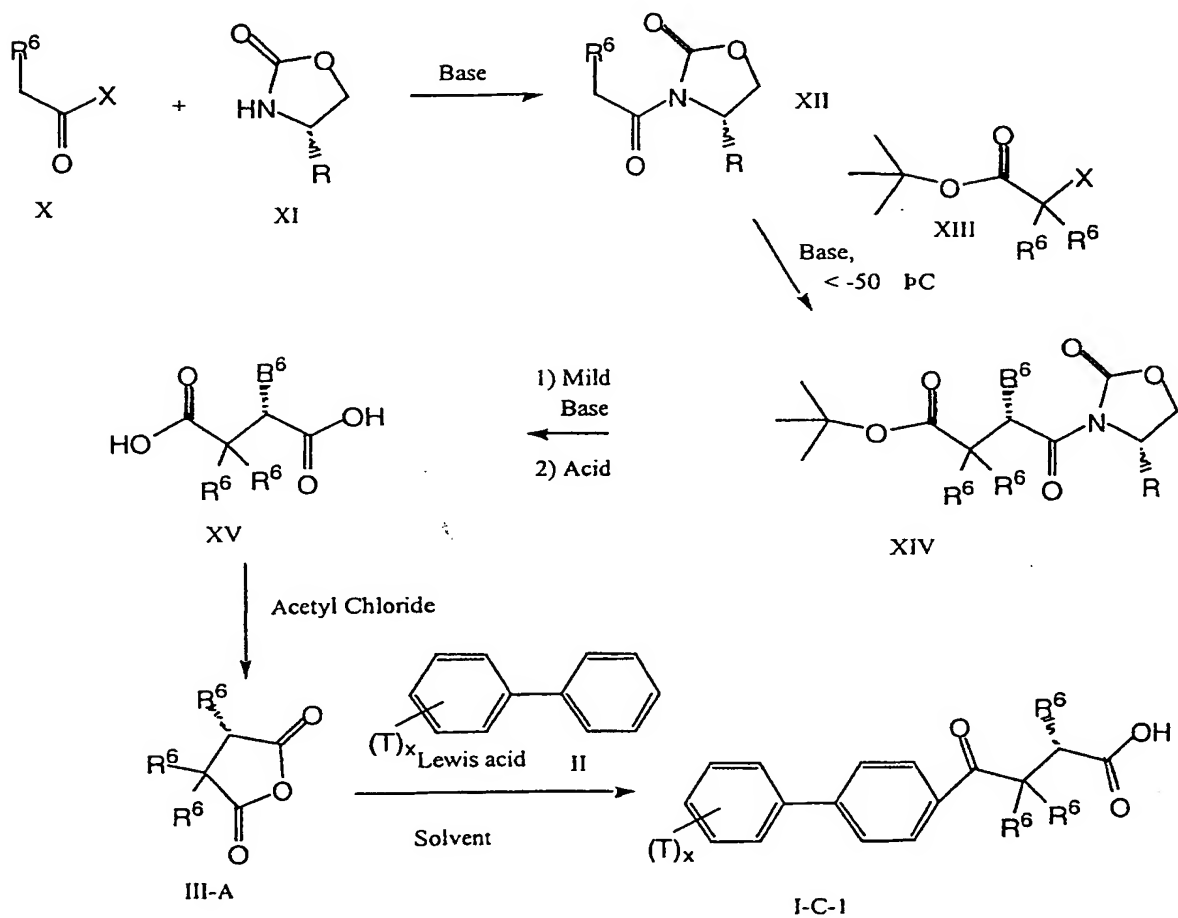
General Method C - Especially useful is the use of chiral HPLC to separate the enantiomers of racemates of key intermediates or final products (see, for example, D. Arlt, B. Boemer, R Grosser and W. Lange, *Angew. Chem. Int. Ed. Engl.* 30 (1991) No. 12). The key intermediates are prepared as pure enantiomers by use of a chiral auxiliary route - see, for example: D.A. Evans, *Aldrichimica Acta*, 15(2), 23 (1982) and other similar references known to one skilled in the art.

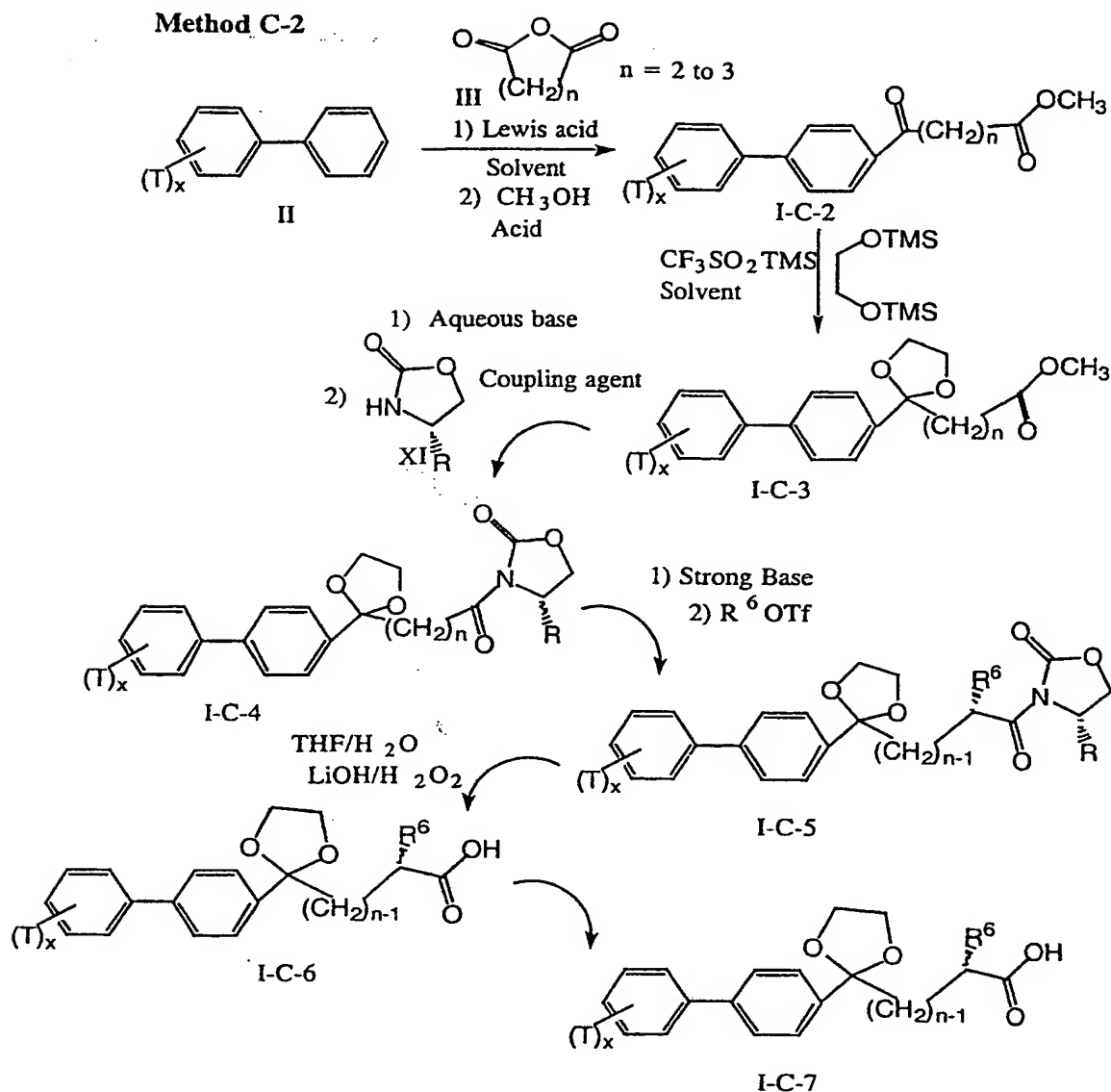
C-1. Acid halide X is reacted with the lithium salt of chiral auxiliary XI (R is often isopropyl or benzyl) to yield intermediate XII, which in turn is alkylated at low temperatures (typically under -50°C) with halo-tert-butylacetyl compound XIII to yield pure isomer XIV. The use of opposite chirality XI yields opposite chirality XIV. Conversion of XIV to the enantiomerically pure diacid XV is accomplished by treatment with lithium hydroxide/hydrogen peroxide in THF/water, followed by acids such as trifluoroacetic acid. The compound XV is then converted to enantiomerically pure anhydride III-A by treatment with acetyl chloride. The use of a Friedel-Crafts reaction as in method A then converts III-A to I-C-1.

C-2. Biphenyl starting material II may also first be reacted in a Friedel-Crafts reaction as earlier described with succinic anhydride followed by Fisher esterification with a lower alcohol such as methanol in the presence of a strong acid such as sulfuric acid to form acyl derivative I-C-2. The carbonyl group of this material is then blocked as a ketal such as that formed by treatment with 1,2-bis(trimethylsilyloxy)ethane in the presence of a catalyst such as trimethylsilyltriflate in a suitable solvent. Many other ketal derivatives and reaction conditions familiar to those skilled in the art can also be used in this step. Basic hydrolysis of the ester followed by reaction of the resultant I-C-3 with XI in the presence of an amide coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide yields amide I-C-4. Reaction of this chiral amide with an alkylating agent such as alkyl or arylalkyl triflate or halide yields enantiomerically enriched product I-C-5 which can be converted to ketal-acid I-C-6 by treatment with a weak base such as lithium

hydroxide/hydrogen peroxide and then to keto acid I-C-7 by treatment with an acid. These deblocking steps can be conducted in either order.

Method C-1

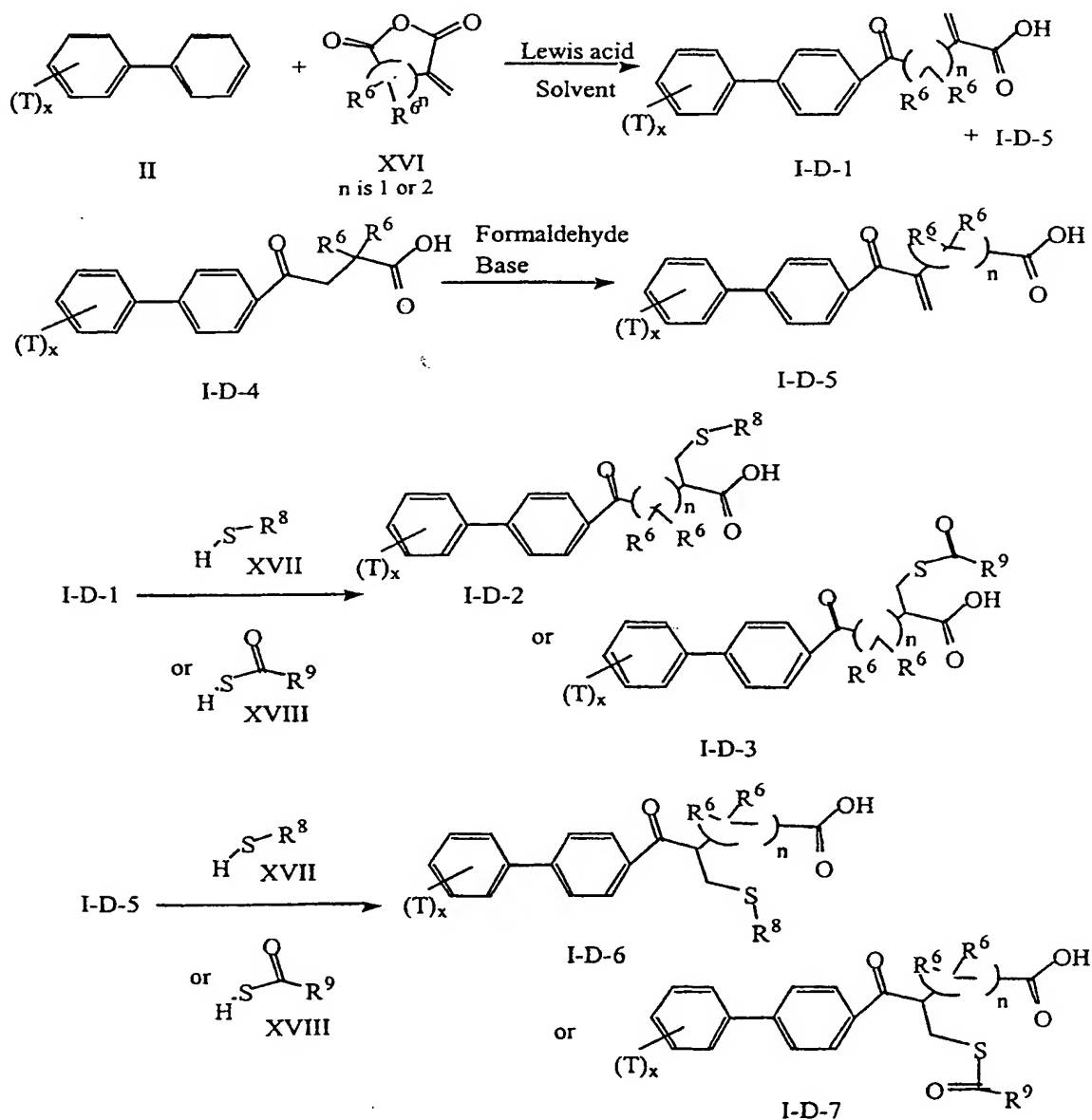




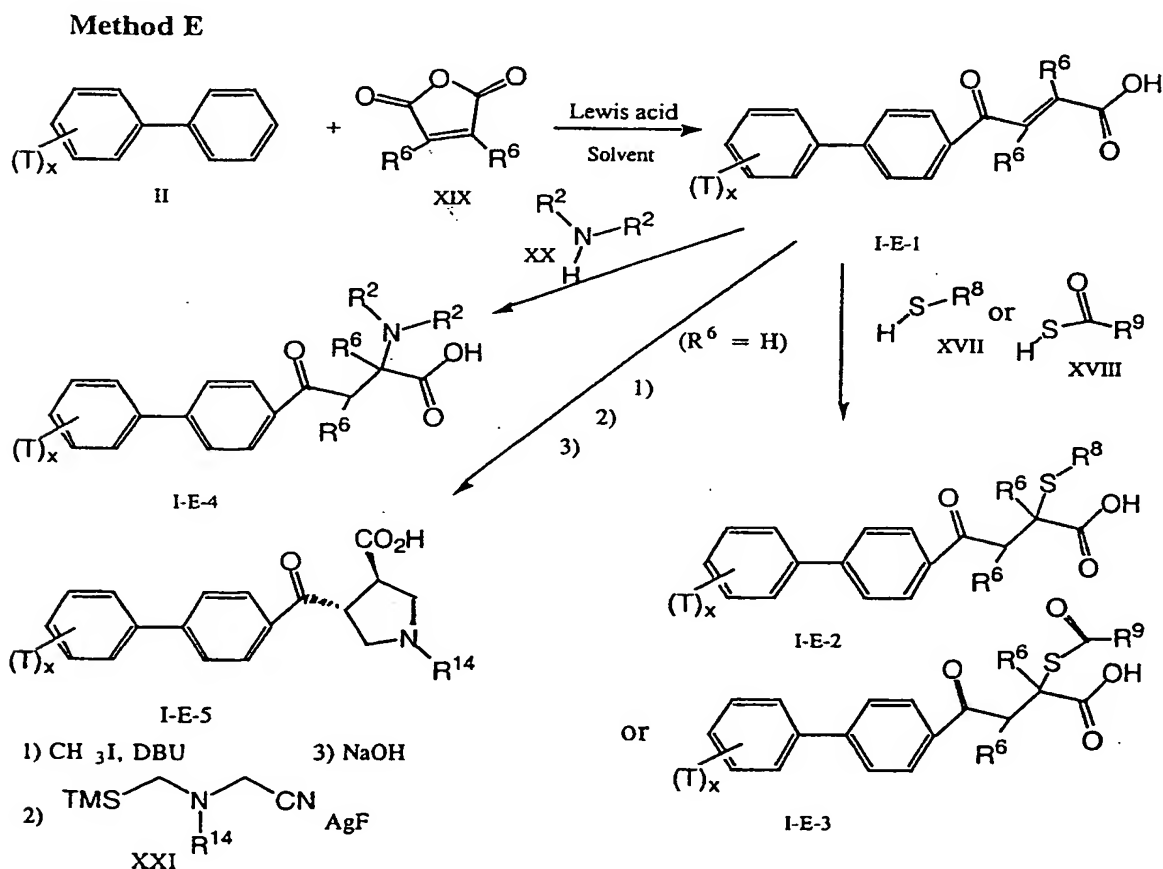
General Method D - Key intermediates in which R^6 are alkyl- or aryl- or heteroaryl- or acyl- or heteroarylcarbonyl-thiomethylene are prepared by methods analogous to those described in the patent publication WO 90/05719. Thus substituted itaconic anhydride XVI ($n = 1$) is reacted under Friedel-Crafts conditions to yield acid I-D-1 which can be separated by chromatography or crystallization from small amounts of isomeric I-D-5. Alternatively, I-D-5 are obtained by reaction of key intermediates I-D-4 (from any of Methods A through C) with formaldehyde in the presence of a base.

Compounds I-D-1 or I-D-5 are then reacted with a mercapto derivative XVII or XVIII in the presence of a catalyst such as potassium carbonate, ethyldiisobutylamine, tetrabutylammonium fluoride or free radical initiators such as azobisisobutyronitrile (AIBN) in a solvent such as dimethylformamide or tetrahydrofuran to yield key intermediates I-D-2, I-D-3, I-D-6 or I-D-7.

Method D



General Method E - Reaction of optionally substituted maleic anhydride XIX under Friedel-Crafts conditions with II yields key intermediate I-E-1, which in turn is reacted with either of mercapto derivatives XVII or XVIII to yield key intermediates I-E-2 or I-E-3, or with substituted amine XX to yield key intermediate I-E-4. Esterification of I-E-1 ($R^6 = H$) with CH_3I/DBU followed by reagent XXI and AgF and then basic hydrolysis yields pyrrolidine key intermediate I-E-5. R^{14} can be various alkyl or arylalkyl groups including benzyl. Reaction of the intermediate ester (from step 2) with benzyloxycarbonyl chloride in THF at reflux followed by hydrolysis yields key intermediates in which R^{14} is benzyloxycarbonyl.



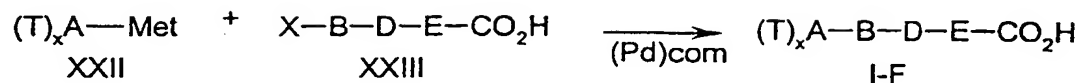
General Method F - Biaryl key intermediates such as those of this application may also be prepared by Suzuki or Stille cross-coupling reactions of aryl or heteroaryl metallic compounds in which the metal is zinc, tin, magnesium, lithium, boron, silicon, copper, cadmium or the like with an aryl or heteroaryl halide or triflate (trifluoro-

romethane-sulfonate) or the like. In the equation below either Met or X is the metal and the other is the halide or triflate. Pd(com) is a soluble complex of palladium such as tetrakis(triphenylphosphine)-palladium(0) or bis-(triphenylphosphine)-palladium(II) chloride. These methods are well known to those skilled in the art. See, for example, A. Suzuki, Pure Appl. Chem., 66, 213 - 222 (1994); A. Suzuki, Pure Appl. Chem., 63, 419 - 422 (1991); and V. Farina and G. Roth, "Metal-Organic Chemistry" Volume 5 (Chapter 1), 1994.

The starting materials XXIII (B = 1,4-phenylene) are readily formed using methods analogous to those of methods A, B or C but using a halobenzene rather than a biphenyl as starting material. When desired, the materials in which X is halo can be converted to those in which X is metal by reactions well known to those skilled in the art such as treatment of a bromo intermediate with hexamethylditin and palladium tetrakis(triphenylphosphine) in toluene at reflux to yield the trimethyltin intermediate.

The starting materials XXIII (B = heteroaryl) are most conveniently prepared by method C but using readily available heteroaryl rather than biphenyl starting materials. The intermediates XXII are either commercial or easily prepared from commercial materials by methods well known to those skilled in the art.

These general methods are useful for the preparation of key intermediates for which Friedel-Crafts reactions such as those of Methods A, B, C, D or E would lead to mixtures with various biaryl acylation patterns. Method F is also especially useful for the preparation of key intermediates in which the aryl groups A or B contain one or more heteroatoms (heteroaryls) such as those compounds that contain thiophene, furan, pyridine, pyrrole, oxazole, thiazole, pyrimidine or pyrazine rings or the like instead of phenyls.

Method F

T, x, A, B, E and D as in Structure I

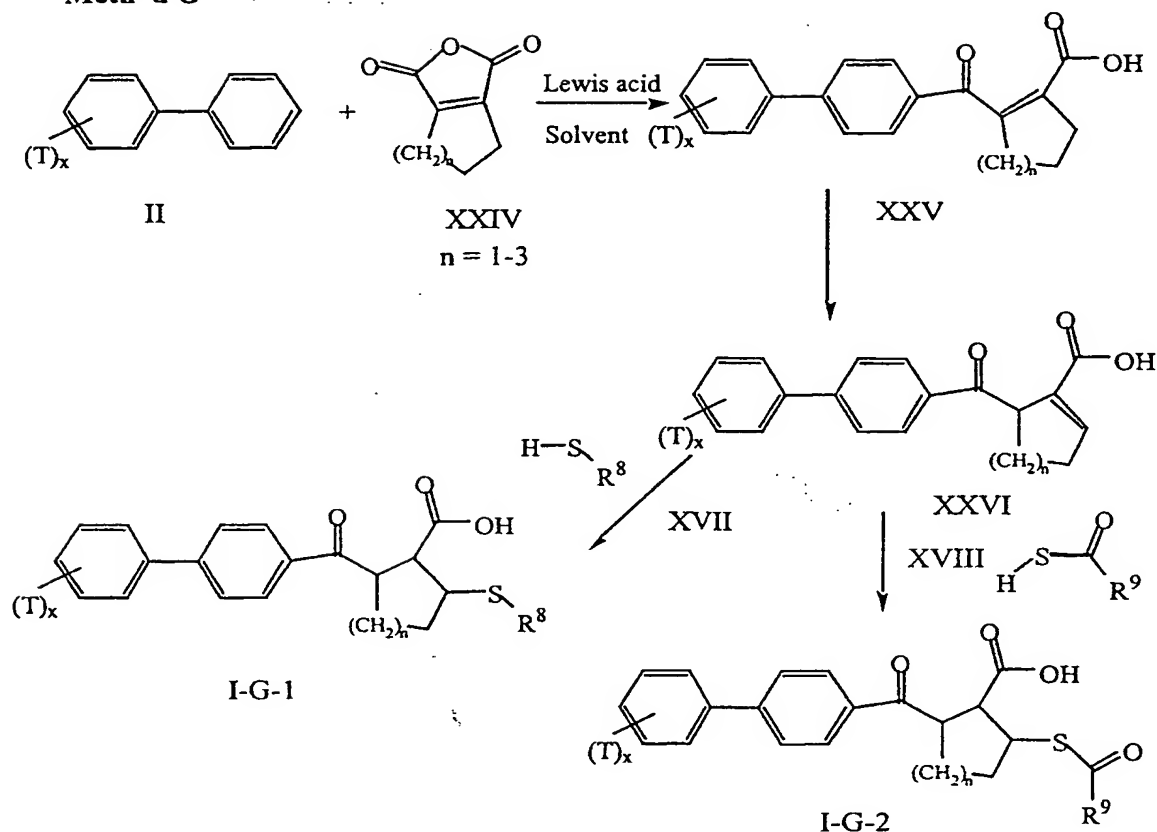
Met = Metal and X = Halide or Triflate

or

Met = Halide or Triflate and X = Metal

5 **General Method G** - When the R⁶ groups of method F form together a 4 - 7 membered carbocyclic ring as in Intermediate XXV below, the double bond can be moved out of conjugation with the ketone group by treatment with two equivalents of a strong base such as lithium diisopropylamide or lithium hexamethylsilylamide or the like followed by acid quench to yield compounds with the structure XXVI. Reaction of XXVI with mercapto derivatives using methods analogous to those of General Method D then leads to key intermediate I-G-1 or I-G-2.

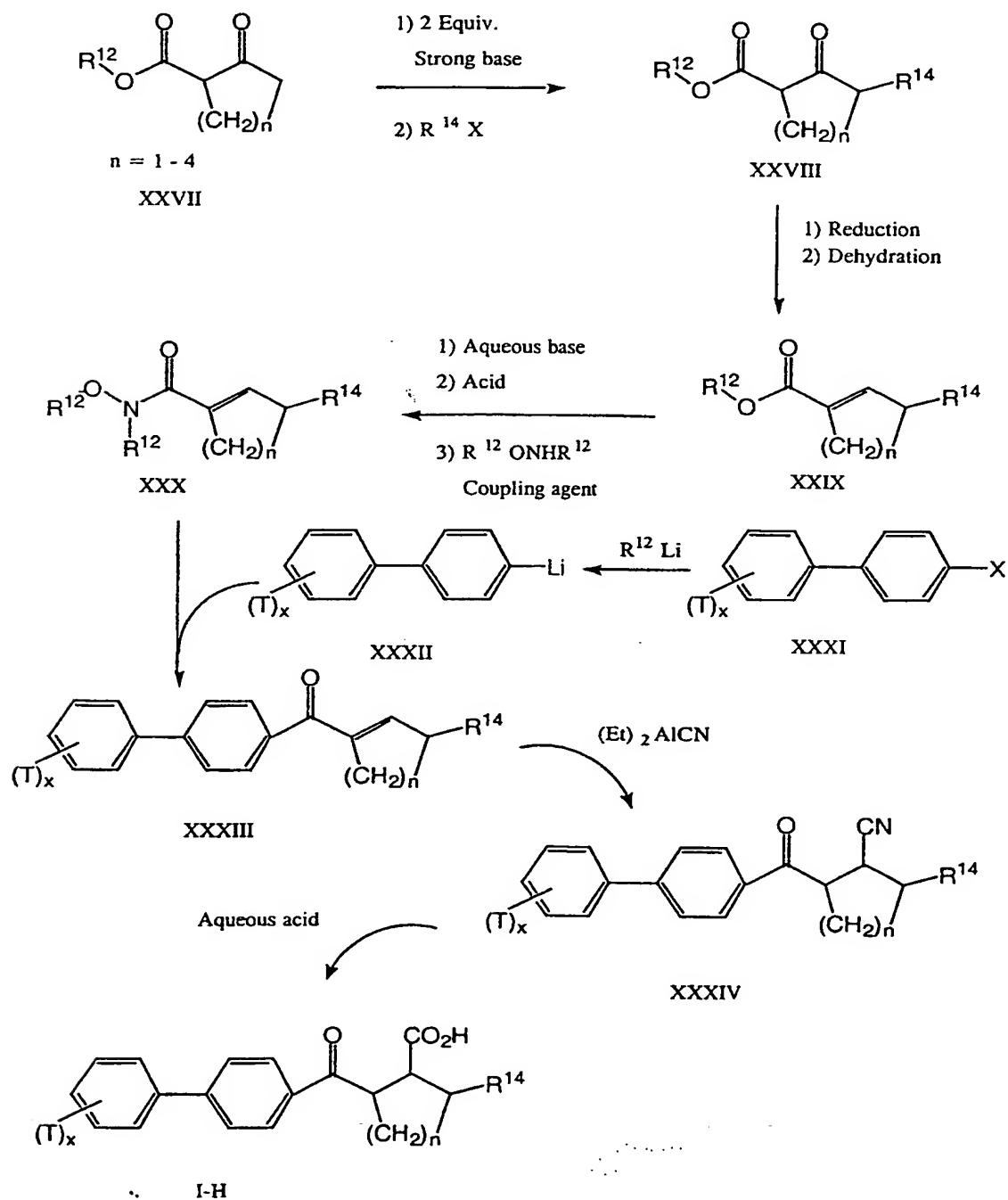
Method G



General Method H - Key intermediates in which two R^6 groups form a 4 - 7 member carbocyclic ring as in I-H below and R^{14} is alkyl or arylalkyl are prepared according to method H. Starting material XXVII is reacted with two equivalents of a strong base such as lithium diisopropylamide (LDA) followed by an alkyl or arylalkyl halide ($R^{14}X$) to yield intermediate XXVIII. This material is then reduced to the alcohol with a reducing agent capable of selective reduction of the ketone such as sodium borohydride, followed by dehydration with triphenylphosphine / diethyl azodicarboxylate (DEAD) in a suitable solvent such as THF at reflux to yield XXIX. Hydrolysis of the ester with aqueous base followed by amide formation with $R^{12}ONHR^{12}$ (R is (C_1-C_4) -alkyl, but usually CH_3) in the presence of a coupling agent such as dicyclohexyldiimide (DCC) yields XXX. Other acyl activating groups well known to those skilled in the art such as acid chlorides or mixed anhydrides could be used instead of XXX. Substituted biphenyl halide XXXI is reacted with an alkyl lithium such as two equivalents of *t*-butyl lithium to yield lithiated biphenyl

XXXII which is then reacted with activated acyl compound XXX. The resultant intermediate XXXIII is then treated with diethylaluminum cyanide to yield intermediate XXXIV which is then hydrolyzed with aqueous acid to yield key intermediate I-H which is purified by chromatography on silica gel to afford pure isomers.

Method H

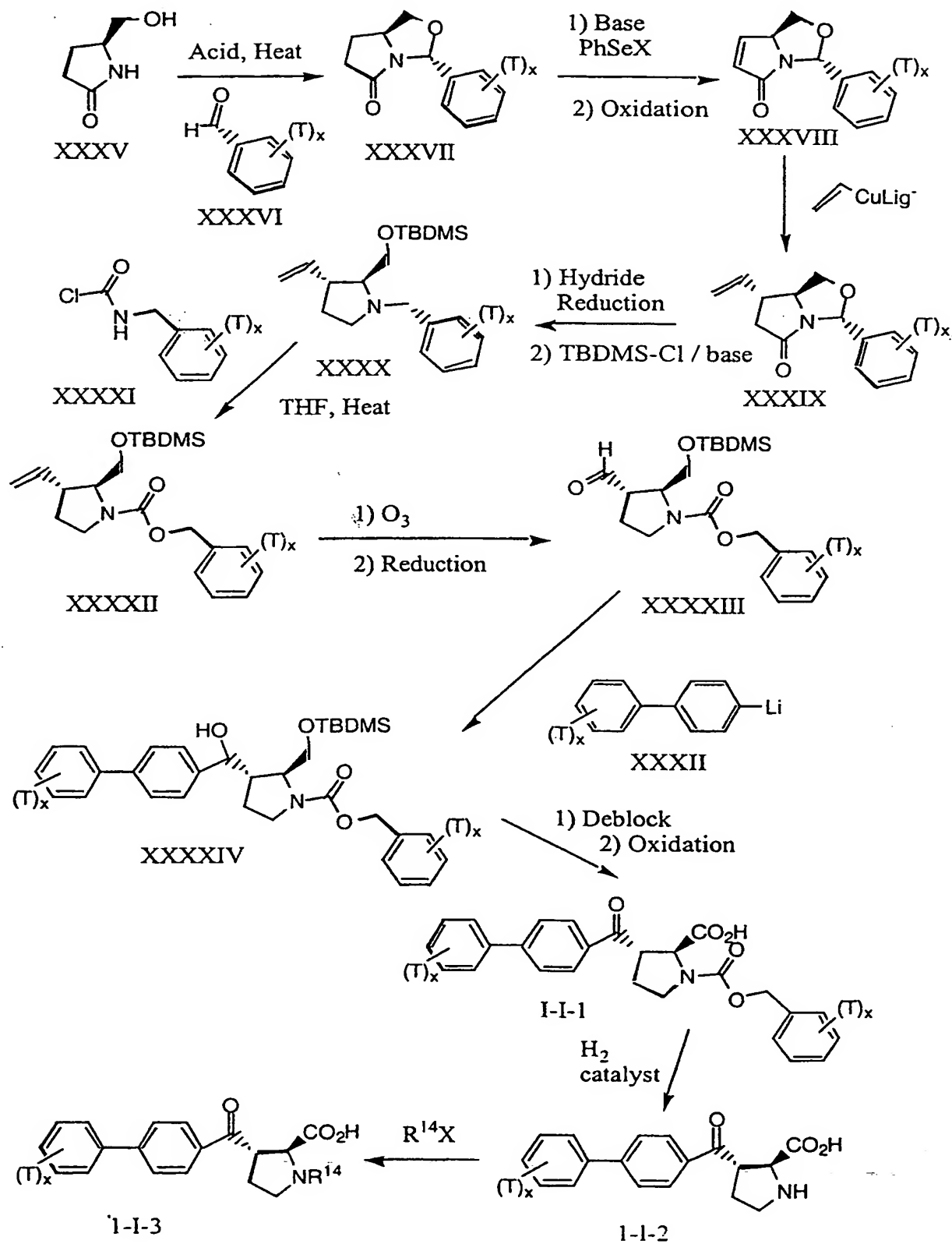


General Method I - Key intermediates in which two R⁶ groups together form a pyrrolidine ring are prepared according to method I. Starting material XXXV (L-pyrroglutaminol) is reacted under acid catalysis with benzaldehyde XXXVI (may be substituted) to yield bicyclic derivative XXXVII. A double bond is then introduced using phenylselenenyl methodology well known to those skilled in the art to yield XXXVIII, which, in turn, is reacted with a vinylcopper (I) complex to yield conjugate addition product XXXIX. Such reactions in which Lig can be, for example, another equivalent of vinyl group or halide are well known to those skilled in the art. Hydride reduction (lithium aluminum hydride or the like) of XXXIX followed by standard blocking with, for example, t-butyltrimethylsilylchloride yields XXXX which in turn is reacted with an optionally substituted benzylchloroformate XXXXI to yield XXXXII. Ozonolysis of this intermediate followed by reductive workup (dimethylsulfide, zinc/acetic acid or the like) leads to aldehyde XXXXIII. Reaction of this aldehyde with a biphenyl organometallic such as XXXII yields alcohol XXXXIV. Deblocking of the silyl group with, for example, tetrabutylammonium fluoride followed by oxidation with, for example, pyridiniumdichromate or the like yields key intermediate 1-I-1 in which R¹⁴ is a carbobenzyloxy group.

Alternatively the carbobenzyloxy group is removed by reaction with hydrogen and a catalyst such as palladium on carbon to yield the unsubstituted key intermediate 1-I-2 optionally followed by N-alkylation to yield key intermediate 1-I-3. These final steps are well known to those skilled in the art. Alternatively the intermediate XXXX can be directly treated with ozone followed by the other steps of this method to yield 1-I-3, in which R¹⁴ is optionally substituted benzyl rather than as in 1-I-1.

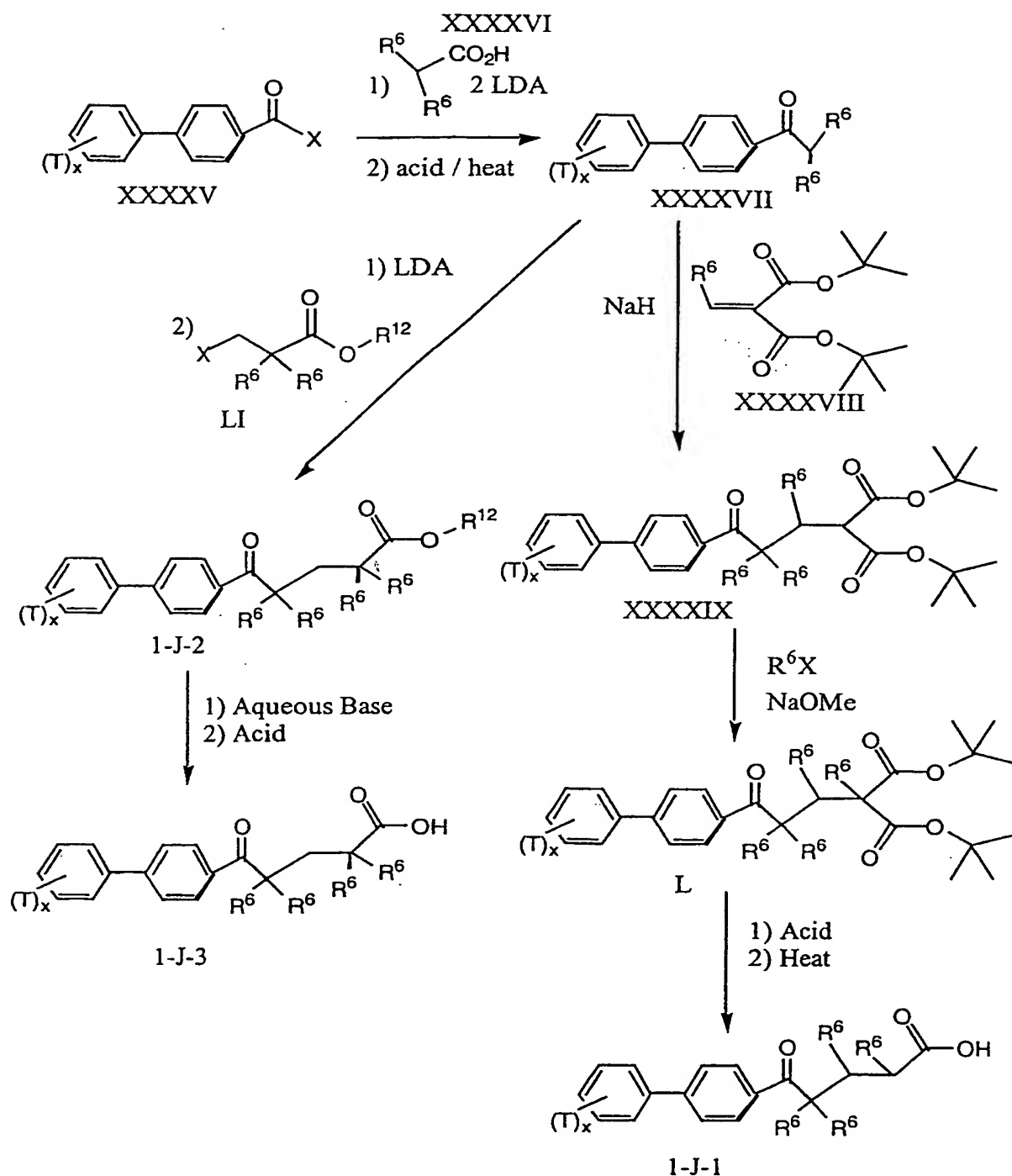
This method is especially useful to prepare single enantiomers because starting material XXXV is available as either the isomer as drawn or as D-pyrroglutaminol to yield enantiomeric products.

Method I



General Method J - The key intermediates in which E represents a substituted chain of 3 carbons are prepared by method J. Intermediates XXXXVII, if not available from commercial sources, are prepared by reaction of an activated biphenylcarboxylic acid derivative XXXXV with substituted acetic acid XXXXVI which has been converted to its bis-anion with two equivalents of a strong base such as LDA followed by heating to decarboxylate the intermediate keto acid. Product XXXXVII is then treated with methylenemalonate derivative XXXXVIII in the presence of a strong base such as sodium hydride to yield substituted malonate XXXXIX. This malonate can be further alkylated under conditions familiar to those skilled in the art to yield L which in turn is treated with acid and then heated to yield key intermediate 1-J-1. Alternatively the final alkylation can be omitted to yield products in which the R⁶ adjacent to the carboxyl is H. Alternatively XXXXVII can be alkylated with 3-halopropionate ester LI in the presence of base such as LDA to yield ester 1-J-2 which can then be hydrolyzed with aqueous base to yield key intermediate 1-J-3 upon treatment with acid. This method is especially useful if any of the groups R⁶ contain aromatic residues.

Method J



Method K - The key intermediates in which two R^6 groups are joined to form a substituted 5-member ring are most conveniently prepared by method K. In this method

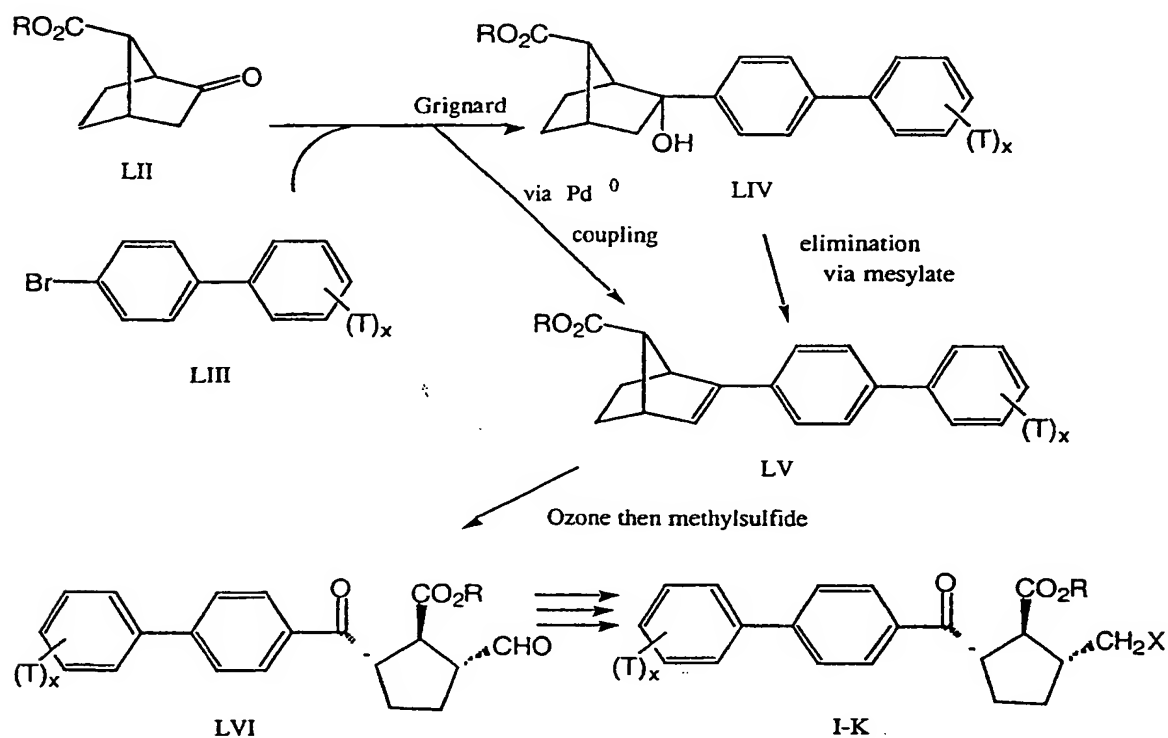
acid LII (R = H) is prepared using the protocols described in *Tetrahedron*, Vol. 37, Suppl., 1981, 411. The acid is protected as an ester (R = benzyl or 2-(trimethylsilyl)ethyl) by use of coupling agents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and procedures well known to those skilled in the art. Substituted bromobiphenyl LIII is converted to its Grignard reagent by treatment with magnesium which is then reacted with LII to yield alcohol LIV. Alcohol LIV is eliminated via base treatment of its mesylate by using conditions well known to those skilled in the art to yield olefin LV. Alternatively LIII is converted to a trimethyltin intermediate via initial metallation of the bromide with n-butyllithium at low temperature (-78°C) followed by treatment with chlorotrimethyltin and LII is converted to an enoltriflate by reaction with 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine in the presence of a strong aprotic base. The tin and enoltriflate intermediates are then coupled in the presence of a Pd⁰ catalyst, CuI and AsPh₃ to yield directly intermediate LV. Ozonolysis of LV (workup with methyl sulfide) yields aldehyde LVI. Alternatively treatment with OsO₄ followed by HIO₄ converts LV to LVI.

Conversion of intermediate LVI to key intermediate I-K is accomplished in several ways depending on the identity of side chain function X. Reaction of LVI with Wittig reagents followed by hydrogenation yields products in which X is alkyl, aryl or arylalkyl. Reduction of aldehyde LVI with LAH yields alcohol I-K (X = OH). The alcohol is converted to phenyl ethers or N-phthalimidoyl compounds by use of the appropriate starting materials and Mitsunobu conditions well known to those skilled in the art; see O. Mitsunobu, *Synthesis*, 1 (1981). Alternatively the alcohol of I-K (X = OH) is converted to a leaving group such as tosylate (X = OTs) or bromide (X = Br) by conditions well known to those skilled in the art and then the leaving group is displaced by sulfur or azide nucleophiles to yield products with X = thioether or azide which in turn is reduced and acylated to yield amides (X = NHAcyl). Direct acylation of the alcohol I-K (X = OH) yields key intermediates in which X = OAcyl and reaction of the alcohol with various alkyl halides in the presence of base yields alkyl ethers (X = OR²). In each case a final step is removal of acid blocking group R

to yield acids ($R = H$) by using conditions which depend on the stability of R and X , but in all cases well known to those skilled in the art such as removal of benzyl by base hydrolysis or of 2-(trimethylsilyl)ethyl by treatment with tetrabutylammonium fluoride.

5

Method K



Suitable pharmaceutically acceptable salts of the compounds of the present invention that contain an acidic moiety include addition salts formed with organic or inorganic bases. The salt forming ion derived from such bases can be metal ions, e.g., aluminum, alkali metal ions, such as sodium or potassium, alkaline earth metal ions such as calcium or magnesium, or an amine salt ion, of which a number are known for this purpose. Examples include ammonium salts, arylalkylamines such as dibenzylamine and *N,N*-dibenzylethylenediamine, lower alkylamines such as methylamine, *t*-butylamine, procaine, lower alkylpiperidines such as *N*-ethylpiperidine, cycloalkylamines such as cyclohexylamine or dicyclohexylamine, 1-adamantylamine,

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benzathine, or salts derived from amino acids like arginine, lysine or the like. The physiologically acceptable salts such as the sodium or potassium salts and the amino acid salts can be used medicinally as described below and are preferred.

5 Suitable pharmaceutically acceptable salts of the compounds of the present invention that contain a basic moiety include addition salts formed with organic or inorganic acids. The salt forming ion derived from such acids can be halide ions or ions of natural or unnatural carboxylic or sulfonic acids, of which a number are known for this purpose. Examples include chlorides, acetates, tartrates, or salts derived from
10 amino acids like glycine or the like. The physiologically acceptable salts such as the chloride salts and the amino acid salts can be used medicinally as described below and are preferred.

15 These and other salts which are not necessarily physiologically acceptable are useful in isolating or purifying a product acceptable for the purposes described below.

20 The salts are produced by reacting the acid form of the invention compound with an equivalent of the base supplying the desired basic ion or the basic form of the invention compound with an equivalent of the acid supplying the desired acid ion in a medium in which the salt precipitates or in aqueous medium and then lyophilizing. The free acid or basic form of the invention compounds can be obtained from the salt by conventional neutralization techniques, e.g., with potassium bisulfate, hydrochloric acid, sodium hydroxide, sodium bicarbonate, etc.

25 The compounds of the present invention are expected to inhibit the matrix metallo-proteases MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-12, MMP-13, and the related protease TACE, as well as the release of $\text{TNF}\alpha$ in vivo, and are therefore expected to be useful for treating or preventing the conditions referred to in the background section. As other MMPs not listed above share a high degree of homology
30 with those listed above, especially in the catalytic site, it is deemed that compounds of the invention should also inhibit such other MMPs to varying degrees. Varying

the substituents on the biaryl portions of the molecules, as well as those of the R⁶ groups of the claimed compounds, is expected to affect the relative inhibition of the listed MMPs. Thus compounds of this general class can be "tuned" by selecting specific substituents such that inhibition of specific MMP(s) associated with specific pathological conditions can be enhanced while leaving non-involved MMPs less affected.

The method of treating matrix metalloprotease-mediated or TNF α release-mediated conditions may be practiced in mammals, including humans, which exhibit such conditions.

The inhibitors of the present invention are contemplated for use in veterinary and human applications. For such purposes, they will be employed in pharmaceutical compositions containing active ingredient(s) plus one or more pharmaceutically acceptable carriers, diluents, fillers, binders, and other excipients, depending on the administration mode and dosage form contemplated.

Administration of the inhibitors may be by any suitable mode known to those skilled in the art. Examples of suitable parenteral administration include intravenous, intra-articular, subcutaneous and intramuscular routes. Intravenous administration can be used to obtain acute regulation of peak plasma concentrations of the drug. Improved half-life and targeting of the drug to the joint cavities may be aided by entrapment of the drug in liposomes. It may be possible to improve the selectivity of liposomal targeting to the joint cavities by incorporation of ligands into the outside of the liposomes that bind to synovial-specific macromolecules. Alternatively intramuscular, intraarticular or subcutaneous depot injection with or without encapsulation of the drug into degradable microspheres e.g., comprising poly(DL-lactide-co-glycolide) may be used to obtain prolonged sustained drug release. For improved convenience of the dosage form it may be possible to use an i.p. implanted reservoir and septum such as the Percuseal system available from Pharmacia. Improved convenience and patient compliance may also be achieved by the use of either injector pens (e.g. the

Novo Pin or Q-pen) or needle-free jet injectors (e.g. from Bioject, Mediject or Becton Dickinson). Prolonged zero-order or other precisely controlled release such as pulsatile release can also be achieved as needed using implantable pumps with delivery of the drug through a cannula into the synovial spaces. Examples include the subcutaneously implanted osmotic pumps available from ALZA, such as the ALZET osmotic pump.

Nasal delivery may be achieved by incorporation of the drug into bioadhesive particulate carriers (<200 μm) such as those comprising cellulose, polyacrylate or polycarbophil, in conjunction with suitable absorption enhancers such as phospholipids or acylcarnitines. Available systems include those developed by DanBiosys and Scios Nova.

Oral delivery may be achieved by incorporation of the drug into tablets, coated tablets, dragées, hard and soft gélatine capsules, solutions, emulsions or suspensions. Oral delivery may also be achieved by incorporation of the drug into enteric coated capsules designed to release the drug into the colon where digestive protease activity is low. Examples include the OROS-CT/Osmet™ and PULSINCAP™ systems from ALZA and Scherer Drug Delivery Systems respectively. Other systems use azo-crosslinked polymers that are degraded by colon specific bacterial azoreductases, or pH sensitive polyacrylate polymers that are activated by the rise in pH at the colon. The above systems may be used in conjunction with a wide range of available absorption enhancers.

Rectal delivery may be achieved by incorporation of the drug into suppositories.

The compounds of this invention can be manufactured into the above listed formulations by the addition of various therapeutically inert, inorganic or organic carriers well known to those skilled in the art. Examples of these include, but are not limited to, lactose, corn starch or derivatives thereof, talc, vegetable oils, waxes, fats, polyols such as polyethylene glycol, water, saccharose, alcohols, glycerin and the like.

Various preservatives, emulsifiers, dispersants, flavorants, wetting agents, anti-oxidants, sweeteners, colorants, stabilizers, salts, buffers and the like are also added, as required to assist in the stabilization of the formulation or to assist in increasing bioavailability of the active ingredient(s) or to yield a formulation of acceptable
5 flavor or odor in the case of oral dosing.

The amount of the pharmaceutical composition to be employed will depend on the recipient and the condition being treated. The requisite amount may be determined without undue experimentation by protocols known to those skilled in the art. Alter-
10 natively, the requisite amount may be calculated, based on a determination of the amount of target enzyme which must be inhibited in order to treat the condition. It is expected that the compounds of the invention generally will be administered in doses in the range of 0.01-100 mg per kg of body weight per day.

15 The matrix metalloprotease inhibitors of the invention are useful not only for treatment of the physiological conditions discussed above, but are also useful in such activities as purification of metalloproteases and testing for matrix metalloprotease activity. Such activity testing can be both *in vitro* using natural or synthetic enzyme preparations or *in vivo* using, for example, animal models in which abnormal
20 destructive enzyme levels are found spontaneously (use of genetically mutated or transgenic animals) or are induced by administration of exogenous agents or by surgery which disrupts joint stability.

Biological Protocols

Inhibitory activities of the compounds of the invention against matrix metalloproteases and production of $\text{TNF}\alpha$ may be determined as described below.

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Preparation of Gelatinase-B (MMP-9):

MMP-9 is isolated modifying the previously described procedures of Hibbs *et al* (J. Biol. Chem., 260, 2493-2500, 1984) and Wilhelm *et al* (J. Biol. Chem., 264, 17213-17221, 1989). Briefly, polymorphonuclear leukocytes (PMN) preparations are isolated as described above from 3 or more units of freshly drawn whole blood. Cells are resuspended in phosphate buffered saline (PBS) containing 100 ng/ml phorbol myristate acetate (PMA) in the presence of 50 mM di-isopropylfluorophosphate (DFP), 1 $\mu\text{g/ml}$ leupeptin and aprotinin, and 1 mg/ml catalase for 1 hr at 37°C. Supernatants are collected by centrifugation (300 x g) and the samples are frozen at -70°C. All chromatographic methods are performed at 4°C. Thawed samples are concentrated 5-fold using an Amicon chamber equipped with a YM-10 membrane. The concentrate is pressure dialyzed against 0.02M Tris-HCl, 0.1 M NaCl, 1 mM CaCl_2 , 1 μM ZnCl_2 , 0.001% Brij-35, 0.02% sodium azide (NaN_3), pH 7.5 and applied to DEAE ion exchange chromatography resin which is previously equilibrated with the same buffer at a flow rate of 0.4 ml/min. The column is extensively washed with the same buffer and gelatinase is eluted as 4 ml fractions from the column with 0.02M Tris-HCl, 0.5 M NaCl, 1 mM CaCl_2 , 1 μM ZnCl_2 , 0.001% Brij-35, 0.02% NaN_3 , pH 7.5. Gelatinase containing fractions are observed by gelatin zymography (see below), loaded onto a gelatin agarose affinity resin and washed with the same buffer. Gelatinase activity is eluted at a flow rate of 1 ml/min from the column as 1 ml fractions with 0.02M Tris-HCl, 1 M NaCl, 1 mM CaCl_2 , 1 μM ZnCl_2 , 0.001% Brij-35, 0.02% NaN_3 , pH 7.5 containing 10% dimethyl sulfoxide (DMSO). The fractions containing gelatinase activity are pooled and dialyzed against 0.005M Tris-HCl, 5mM NaCl, 0.5 mM CaCl_2 , 0.1 μM ZnCl_2 , 0.001% Brij-35, pH 7.4. The protein content associated with material is determined

with a micro-BCA assay (Pierce, Rockford, IL), lyophilized and reconstituted to a desired working concentration (100 µg/ml).

Preparation of Gelatinase-A (MMP-2):

5

Gelatinase A (MMP-2) is prepared using a vaccinia expression system according to the method of R. Fridman, et al., *J. Biol. Chem.*, 267, 15398 (1992).

Preparation of Recombinant Truncated Prostromelysin (MMP-3):

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Truncated Prostromelysin-257 is expressed in a soluble form in E.coli as described by Marcy et al., *Biochemistry*, 30, 6476-6483, 1991. Soluble truncated prostromelysin is purified by a modification of the monoclonal antibody affinity chromatography method described by Housley et al., *J. Biol. Chem.*, 268, 4481-87, 1993.

15

P218 Quenched fluorescence Assay for MMP-3 Inhibition:

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This assay was originally described by Knight et al., *FEBS Letters*, 296, 263-266, 1992, for a related substrate. The assay is run continuously in a 3.0ml cuvette using a Perkin-Elmer LS 50 B Spectrofluorimeter at 25 °C in a final volume of 2.0 mls. P218 substrate (10mM) in 100% DMSO is diluted to a final concentration of 2.0 micromolar (µM) into assay buffer: 50mM MES, pH 6.5 containing 150mM NaCl, 10mM CaCl₂, 0.005% Brij-35, and 1%(v/v) DMSO. Test compounds(10mM) in DMSO are diluted in assay buffer at an initial concentration of 10 to 100 micromolar. These are diluted to a final concentration in the assay from 10 nM to 1 µM depending upon their potency previously determined in primary thiopeptide assay described above. The reaction is initiated by the addition of recombinant stromelysin (MMP-3) at a final concentration of 1.0 nM. Upon peptide cleavage, the fluorescent MCA group is detected using an excitation wavelength of 328 nanometers and an emission wavelength of 393 nanometers. The assay is linear from 0.2 to 5nM MMP-3 concentration and percent inhibition is calculated as described above for the pri-

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mary thiopeptilide assay and IC₅₀ values are determined by a linear regression analysis of percent inhibition versus log drug concentration. The peptide sequence of the MCA substrate, hereinafter designated P218, is shown below:

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MCA-Pro-Lys-Pro-Leu-Ala-Leu-DPA-Ala-Arg-NH₂

P218

For MMP-3, this substrate has a K_m of 16 μM at pH 6.5 and a k_{cat}/K_m value of 56,000 $\text{M}^{-1}\text{sec}^{-1}$.

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P218 Quenched Fluorescence Assay for MMP-12 Inhibition:

This assay is adapted from the one described by Knight et al., FEBS Letters, 296, 263-266 (1992) for MMP-3 and a related substrate. - The rate of hydrolysis of the synthetic substrate H-MCA-Pro-Lys-Pro-Leu-Ala-Leu-DPA-Ala-Arg-NH₂ (P218) by human recombinant MMP-12 is monitored fluorometrically, using an excitation wavelength of 340 nm and an emission wavelength of 395 nm, in the presence or absence of the test compounds. The assay is carried out in buffer containing 50 mM HEPES and 10 mM CaCl₂ at pH 7.0. The substrate is made up initially in 100% DMSO to a concentration of 1×10^{-2} M, then diluted in assay buffer to a final concentration of 20 μ M. Test compounds (10 mM in DMSO) are diluted in assay buffer at an initial concentration of 0.3-1000 nM. These are diluted to a final concentration in the assay from 0.03 nM to 100 nM. The reaction is initiated by the addition of substrate at a final concentration of 20 μ M. The total assay volume in a 96 well microtitre plate is 150 μ l. Cleavage of the substrate between the Leu-Ala residues allows the fluorescence of the MCA group to be detected on a fluorometer (Cytofluor II) following excitation at 340 nm and emission at 395 nm. Change in fluorescence is continually monitored for a 40 min period.

The K_i 's are calculated using the method described by Williams and Morrison, Methods in Enzymology, 63, 437-467 (1979) to measure K_i apparent for tight binding inhibitors, and is summarised as follows:

$$[I]_0 / (1 - v_i/v_0) = K_{i \text{ apparent}} \times v_i / v_0 + [E]_0$$

5 $[I]_0$ and $[E]_0$ are inhibitor and enzyme concentrations, and v_i / v_0 are reaction velocities with / without inhibitor. $[I]_0$ is equal to IC_{50} when v_i is half v_0 , so that:

$$IC_{50} = 0.5 \times [E]_0 + K_{i \text{ apparent}}$$

10 IC_{50} 's are determined at each enzyme concentration (0.044-0.98 $\mu\text{g/ml}$) using Xlfit software. $K_{i \text{ apparent}}$ is then determined graphically from the plot of IC_{50} versus MMP-12 concentration, using the intercepts to estimate $K_{i \text{ apparent}}$. Thus, intercept values at $IC_{50} = 0$ and $[E]_0 = 0$ are equal to $-2 \times K_{i \text{ apparent}}$ and $K_{i \text{ apparent}}$, respectively. IC_{50} values are calculated using % inhibition values at each enzyme concentration, ensuring data is taken from the linear part of the reaction rate curves. The K_i can then
15 be calculated from the equation:

$$K_i = K_{i \text{ apparent}} / (1+S)/K_m$$

20 where S = substrate concentration (20 μM) and K_m = dissociation constant (5.4 μM).

Automated MMP Profiling Assay

25 This assay is run with a protocol analogous to that reported for MMP-3 inhibition using the synthetic peptide P218 and each of the three enzymes and measuring quenched fluorescence. This assay can be run with each invention compound with the three enzymes in parallel as adapted for a 96-well microtitre plate using a Hamilton AT ® workstation.

The following examples illustrate the selectivity of compounds of the invention for specific human MMPs:

Example	Potency [K_i , nM] vs. MMP-x							
	1	2	3	7	8	9	12	13
4	639	0.5	3.7	>3000	7.5	0.7	0.3	5.6
2	>3000	3.2*	60*	38% inh. at 30 nM	21.6*	1.2	0.03	70*

* IC_{50} [nM]

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LPS Induced $TNF\alpha$ Production in Mice

The *in vivo* inhibitory properties of selected compounds can be determined using a murine LPS induced $TNF\alpha$ production *in vivo* model. BALB/c mice (Charles River Breeding Laboratories; Kingston, NY) in groups of ten are treated with either vehicle or compound. After one hour, endotoxin (E. coli lipopolysaccharide (LPS) 100 mg) is administered intraperitoneally (i.p.). After 90 min, animals are euthanized by carbon dioxide asphyxiation and plasma is obtained from individual animals by cardiac puncture into heparinized tubes. The samples are clarified by centrifugation at 12,500 x g for 5 min at 4 °C. The supernatants are decanted to new tubes, which are stored as needed at -20 °C. $TNF\alpha$ levels in sera are measured using a commercial murine TNF ELISA kit (Genzyme).

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Other embodiments of the invention will be apparent to the skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

Inhibition of Acute EAE Induction in Mice

Acute EAE (Experimental Autoimmune Encephalomyelitis) is induced by immunization of female SJL-mice with an encephalitic fragment of the myelin constituent proteolipid protein (PLP₁₃₉₋₁₅₁) dissolved in Freund's Complete Adjuvant and additional treatment (i.v.) with *Bordetella pertussis*. EAE-diseased mice develop clinical signs around 10 days after immunization which are accompanied by rapid loss of body weight and which resolve between day 16 and 20. Histopathologically this acute disease is characterized by CNS perivascular and parenchymal inflammation and, if at all, minimal demyelination. Infiltrates are mostly composed of T-cells and macrophages.

Animals (n=5) were treated with Example 4. The compound was administered intraperitoneally twice daily for 20 days at 1, 3, and 10 mg/kg and treatment started at the day of disease induction. The compound was dissolved in Labrafil M 1944CS and the injection volume was 100 µl.

The compound dose-dependently inhibited EAE induction (Figure 1). This experiment clearly indicates the therapeutic potential of the compounds of this invention for the treatment of MS.

Inhibition of Acute EAE Induction in Rats

Acute EAE is induced in female Lewis rats by inoculation of a spinal cord-adjuvant emulsion into each hind paw of the animals. Animals show signs of disease (body weight loss, neurological deficits) starting around day 10 after immunization and resolving between days 17-23.

Animals are treated by per os (p.o.) administration of the test compound. Treatment starts on day 6 post inoculation and stops on day 17. The compound is administered

at 3 different doses (e.g. 1, 10, 30 mg/kg) once daily. Body weight and appearance of neurological signs are checked on a daily basis.

Inhibition of Chronic EAE Induction in Mice

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Chronic relapsing EAE is induced by adoptive transfer of PLP₁₃₉₋₁₅₁-responsive lymph node cells to naive female SJL/J recipient mice by injection into the tail vein. 6-8 days later, the mice develop paralysis and incontinence, acute symptoms which correspond to a period of intense inflammation, demyelination and some Wallerian degeneration in the central nervous system. The acute phase peaks from 14-20 days post transfer (dpt) of lymph node cells is followed by remission. The chronic phase of EAE, characterized by spontaneous relapses with severe clinical symptoms, occurs after 21 dpt.

10

15

The test compound is administered daily by p.o. application at 3 different doses (e.g. 1, 10, 30 mg/kg). Treatment starts on day 21 post transfer and stops on day 78. Neurological impairment in EAE mice is evaluated every 1-4 days after disease induction. The clinical scores of each individual animal are used to score relapses and to calculate relapse frequency and mean clinical score.

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Abbreviations

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DMF	dimethylformamide
RT	room temperature
THF	tetrahydrofuran
TBME	tertiary butyl methyl ether

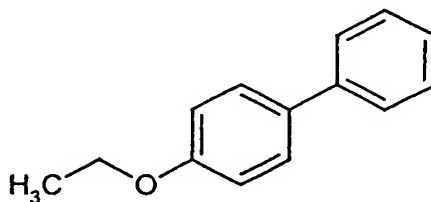
Preparation Examples

Example 1

5 *(rac)*-2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid

Intermediate 1A

4-Ethoxy-1,1'-biphenyl



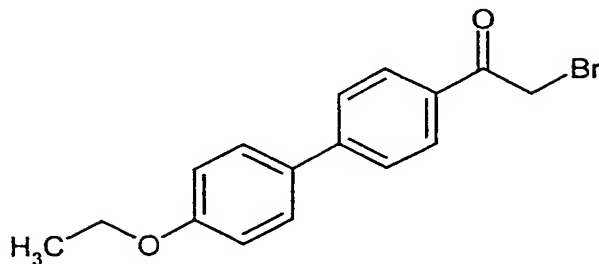
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Iodoethane (68.7 g, 35,57 mL, 440.6 mmol) was added to a suspension of 50 g (170.2 mmol) of 4-hydroxy-1,1'-biphenyl and 40.6 g (293.75 mmol) K_2CO_3 in 60 mL acetone. The resulting reaction mixture was stirred under reflux for 16 hours. After cooling to room temperature the acetone was removed under reduced pressure, the residue was dissolved in ethyl acetate and extracted with water. The aqueous layers were extracted 3 times with ethyl acetate, the combined organic phases dried (Na_2SO_4) and evaporated to yield 56 g of the desired compound as a colorless solid.

20

Yield: 56 g (96 %)

1H -NMR (DMSO- d_6): 7.55-7.65 (m, 4H), 7.42 (t, $J=8$ Hz, 2H), 7.3 (t, $J=8$ Hz, 1H), 6.95-7.05 (m, 2H), 4.07 (q, $J=7$ Hz, 2 H), 1.35 (t, $J=7$ Hz, 3H)

Intermediate 1B*2-bromo-1-(4'-ethoxy[1,1'-biphenyl]-4-yl)-1-ethanone*

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A solution of 56 g (282 mmol) of Intermediate 1A in 1.5 L CH₂Cl₂ was cooled to 0°C and placed under argon. Bromoacetyl bromide (85.5g, 36,8 mL, 423 mmol) was added, and then AlCl₃ (37.41 g, 280.53 mmol) was added in portions over 60 min. After the addition was complete, the mixture was stirred for 20 h, warming to RT. The mixture was then poured slowly into a stirred mixture of 2 kg ice/500ml conc. HCl. The organic layer was separated, , washed with 2N HCl and water, dried (Na₂SO₄) and evaporated. The crude product was purified by recrystallization (acetonitril) to give 49.3g (54%) white solid.

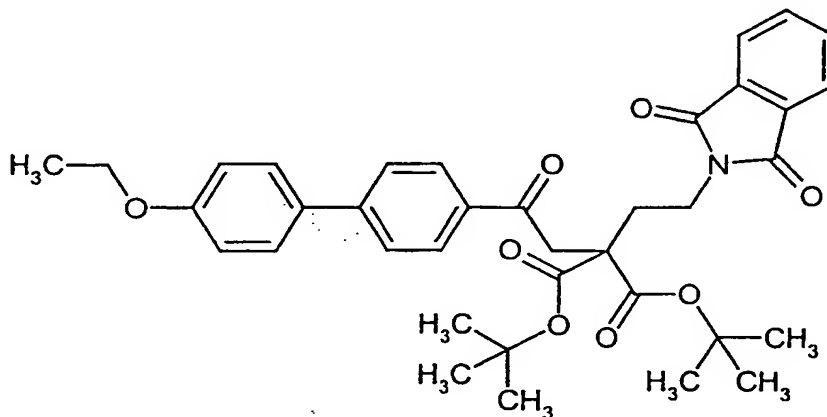
¹H-NMR (DMSO- d₆): 8.08 (d, J=8Hz, 2H), 7.81 (d, J=8Hz, 2H), 7.73 (d, J=8Hz, 2H), 7.06 (d, J=8Hz, 2H), 4.95 (s, 2H), 4.1 (q, J=7Hz, 2H), 1.36 (t, J=7Hz, 3H)

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Intermediate 1C

*Di(tert-butyl) 2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-2-[2-(4'-ethoxy-
[1,1'-biphenyl]-4-yl)-2-oxoethyl]malonate*

5



10

A solution of Intermediate 5F (3.2 g, 10 mmol) in 50 mL DMF was added dropwise to a suspension of NaH (500 mg, 12.5 mmol) in 20 mL DMF and stirred for 30 min at RT. Intermediate 1B (3.9 g, 10 mmol) in 30 ml DMF was added slowly and the resulting mixture was stirred for 4 h at RT. The reaction was quenched with saturated NH_4Cl solution, extracted twice with diethyl ether, washed with saturated NaHCO_3 , water and brine, dried (Na_2SO_4) and evaporated. The crude product was purified using flash chromatography (hexane / ethyl acetate : 1 / 1).

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Yield: 4.96 g (71 %)

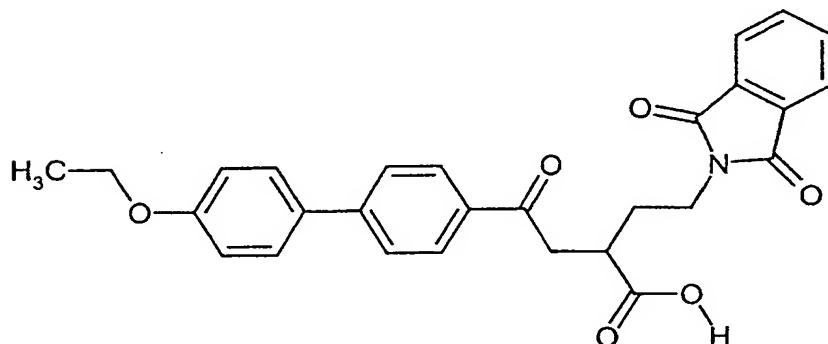
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$^1\text{H-NMR}$ (DMSO- d_6): 8.02 (d, $J=8\text{Hz}$, 2H), 7.68-7.81 (m, 8H), 7.05 (d, $J=8\text{Hz}$, 2H), 4.1 (q, $J=7\text{Hz}$, 2H), 3.72 (s, 2H), 3.55-3.65 (m, 2H), 2.26-2.87 (m, 2H), 1.33-1.4 (m, 18H)

Example 1

(rac)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid

5



2.2 g (3.51 mmol) of Intermediate 1C was added in one portion to a cooled (0°C) 1:1 mixture of CH₂Cl₂ and trifluoroacetic acid. The reaction mixture was stirred overnight at RT, evaporated and dried under vacuum. The residue was dissolved in 5 mL dioxane and heated for 5 h under reflux. The reaction mixture was evaporated, the residue triturated with diethyl ether, stirred for 15 min and filtered. The remaining solid was dried under vacuum.

Yield: 1.21 g (73 %)

¹H-NMR (d₆-DMSO): 12.28 (s, 1H), 8.02 (d, J=8Hz, 2H), 7.67-7.9 (m, 8H), 7.05 (d, J=8Hz, 2H), 4.1 (q, J=7Hz, 2H), 3.72 (t, J=7.5Hz, 2H), 3.49 (dd, J=17.5Hz, J=8Hz, 2H), 3.28 (dd, J=17.5Hz, J=5Hz, 2H), 2.78-2.95 (m, 1H), 1.76-2.13 (m, 2H), 1.38 (t, J=7Hz, 3H)

The racemate of Example 1 was separated into its pure enantiomers via chiral HPLC using a commercially available 5 µm Kromasil KR 100-5-CHI-DMB phase. A solvent mixture consisting of 50% iso-hexane and 50% of a tert-butylmethyl ether / dichloromethane / glacial acetic acid mixture (480:40:1) was employed at a constant flow rate of 25 ml/min.

25

Example 2

(+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid

5

Faster eluting enantiomer:

Yield: 374 mg (42 %)

$[\alpha]^{23}_{\text{D}} + 6.33^{\circ}$ (c=0.47 in THF)

10

Example 3

(-)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid

15

Slower eluting enantiomer:

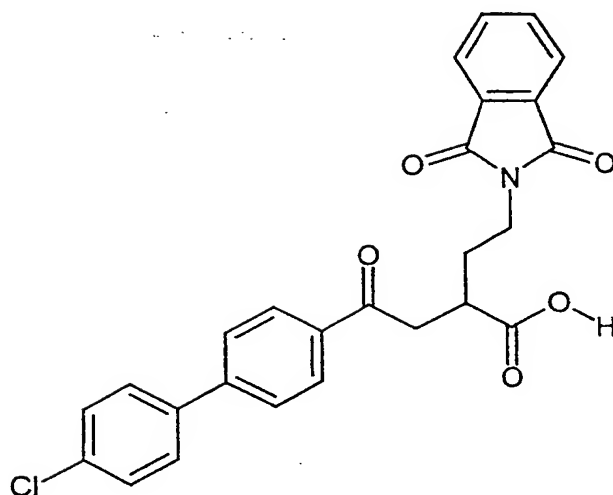
Yield: 321 mg (36%)

$[\alpha]^{23}_{\text{D}} - 5.6^{\circ}$ (c=0.5 in THF)

Example 4

20

(+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid



The compound of Example 4 was prepared according to the procedure given for Example 268 in WO 96/15096.

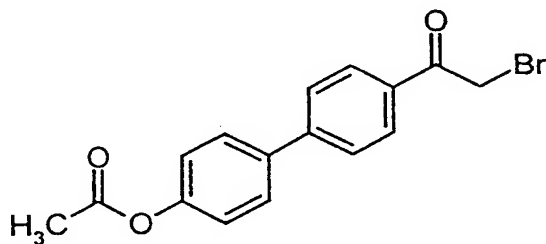
5 $[\alpha]^{23}_D + 5.55^\circ$ (c=0.525 in THF)

Example 5

10 *(rac)-4-[4'-(Acetyloxy)[1,1'-biphenyl]-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-ethyl]-4-oxobutanoic acid*

Intermediate 5A

15 *4'-(2-Bromoacetyl)[1,1'-biphenyl]-4-yl acetate*



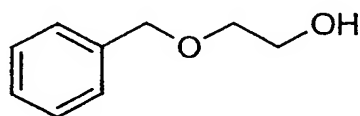
A solution of 50 g (236 mmol) of [1,1'-biphenyl]-4-yl acetate in 500 ml dichloromethane was placed under argon and cooled to 0°C. Bromoacetyl bromide (31.6 ml, 363 mmol) was added, followed by aluminium chloride (94.3 g, 707 mmol) which was added in portions under vigorous stirring over 30 min. The resulting mixture was stirred at 0°C for a further 30 min and at room temperature overnight. The mixture was then slowly poured into 500 ml of cold 10% HCl and extracted three times with dichloromethane. The organic layer was dried over Na₂SO₄, filtered and evaporated. The residue was triturated with 1:1 diisopropyl ether / isopropanol, filtered, and the remaining solid dried under vacuum.

Yield: 73.3 g (93.4%)

¹H-NMR (CDCl₃): δ = 2.34 (s, 3 H), 4.48 (s, 2 H), 7.21 (m, 2 H), 7.66 (m, 4 H), 8.08 (m, 2 H).

Intermediate 5B

2-(Benzyloxy)-1-ethanol



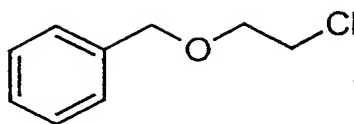
Ethylene glycol (742.5 g, 11.96 mol) was added to a solution of sodium hydroxide pellets (475.2 g, 11.88 mol) in 450 ml of water kept at 80°C. Benzyl chloride (302.8 g, 2.39 mol) was then added at 65°C, and the resulting suspension was vigorously stirred at 120°C overnight. After cooling to room temperature, the mixture was poured into ice-water and extracted five times with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated. The remaining residue was then distilled under vacuum and the relevant fractions (bp. 95-125°C at 0.1-1 mbar) collected.

Yield: 175 g (48.1%) of a colourless liquid.

$^1\text{H-NMR}$ (CDCl_3): $\delta = 2.09$ (tr, 1 H), 3.60 (m, 2 H), 3.77 (m, 2 H), 4.56 (s, 2 H), 7.35 (m, 5 H).

5 Intermediate 5C

Benzyl 2-chloroethyl ether



10

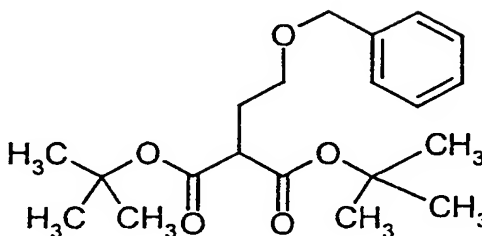
Thionyl chloride (41.2 ml, 567.6 mmol) was slowly added to a mixture of Intermediate 5B (90 g, 80% purity, 473.1 mmol) and N,N-dimethyl aniline (76.5 ml, 597.5 mmol) while keeping the reaction temperature at 50°C by ice-water cooling. After stirring at 50°C for 1 h, further portions of N,N-dimethyl aniline (15.3 ml, 119.5 mmol) and thionyl chloride (8.2 ml, 113.5 mmol) were added, and the mixture was stirred at 50°C for another 2 h and at room temperature overnight. The solution was then poured into a mixture of ice-water (200 ml) and conc. HCl (100 ml) and extracted three times with dichloromethane. The combined organic layers were washed twice with 10% HCl and twice with water, dried over Na_2SO_4 , filtered and evaporated. The remaining residue was then distilled under vacuum (water pump) and the relevant fractions collected.

20

Yield: 69.1 g (85.6%) of a colourless liquid.

25

$^1\text{H-NMR}$ (CDCl_3): $\delta = 3.69$ (m, 4 H), 4.59 (s, 2 H), 7.35 (m, 5 H).

Intermediate 5D*Di(tert-butyl) 2-[2-(benzyloxy)ethyl] malonate*

5

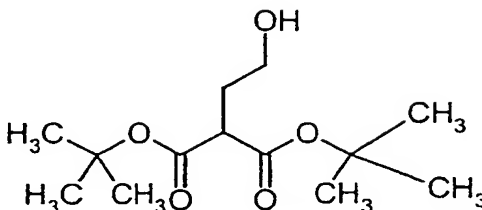
Di(tert-butyl) malonate (151.4 g, 686 mmol) was added dropwise at 50°C to a suspension of potassium tert-butyrate (77 g, 686 mmol) in 500 ml of tert-butanol. Sodium iodide (10.33 g) was then added, followed by dropwise addition of Intermediate 5C (117.1 g, 686 mmol) at 40-50°C. The resulting thick suspension was stirred at 70°C for two days. During this time, two further portions of potassium tert-butyrate (15.4 g each, 70 mmol) were added. The mixture was then poured into ice-water and extracted three times with diethyl ether. The organic layers were dried over Na₂SO₄, filtered and evaporated. The crude product was finally purified by column chromatography using a cyclohexane / ethyl acetate gradient (70:1 -> 15:1).

15

Yield: 134 g (55.8%) of a colourless oil.

¹H-NMR (DMSO-d₆): δ = 1.38 (s, 18 H), 1.96 (q, 2 H), 3.31 (tr, 1 H), 3.41 (tr, 2 H), 4.43 (s, 2 H), 7.31 (m, 5 H).

20

Intermediate 5E*Di(tert-butyl) 2-(2-hydroxyethyl) malonate*

5

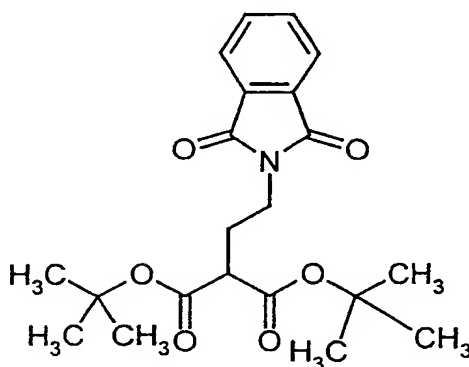
A solution of Intermediate 5D (46.58 g, 132.9 mmol) in 300 ml ethanol was hydrogenated at atmospheric pressure in the presence of 10% palladium on charcoal (2.0 g). After stirring for 3 h at room temperature, another 1.0 g portion of palladium catalyst was added, and stirring was continued at room temperature overnight. The mixture was then filtered through celite, evaporated, and the crude product purified by column chromatography using a dichloromethane / methanol gradient (70:1 - > 30:1).

15 Yield: 23.3 g (67.2%) of a pale yellow oil.

¹H-NMR (CDCl₃): δ = 1.47 (s, 18 H), 1.96 (tr, 1 H), 2.08 (q, 2 H), 3.36 (tr, 1 H), 3.72 (q, 1 H).

Intermediate 5F

Di(tert-butyl) 2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl] malonate



5

To a stirred solution of Intermediate 5E (30.0 g, 115.2 mmol) in 255 ml of dry THF were added successively phthalimide (21.4 g, 144.1 mmol), triphenyl phosphine (35.1 g, 132.5 mmol) and, at 0°C, diethyl azodicarboxylate (22.1 g, 126.8 mmol). The resulting solution was stirred overnight while warming up to room temperature, then diluted with ethyl acetate and washed twice with water and with brine. The organic phase was dried over Na₂SO₄, filtered and evaporated. The crude product was finally purified by column chromatography using a cyclohexane / dichloromethane / ethyl acetate gradient (7:1:1 - > 5:1:1).

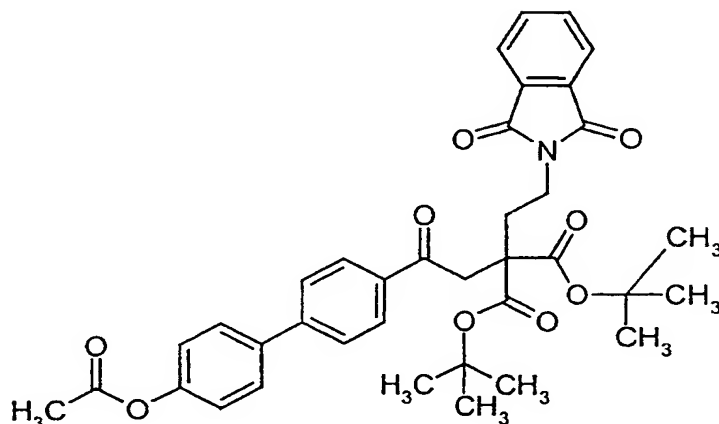
15 Yield: 10.02 g (22.3%) of a white solid.

¹H-NMR (DMSO-d₆): δ = 1.37 (s, 18 H), 2.03 (q, 2 H), 3.30 (tr, 1 H), 3.63 (tr, 2 H), 7.85 (m, 4 H).

Intermediate 5G

Di(tert-butyl) 2-{2-[4'-(acetyloxy)[1,1'-biphenyl]-4-yl]-2-oxoethyl}-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl] malonate

5



Under argon, a solution of Intermediate 5F (6.5 g, 16.69 mmol) in 60 ml of dry THF was added dropwise at 0°C to a suspension of sodium hydride (0.51 g, 80% suspension in mineral oil, 16.86 mmol) in 30 ml of dry THF. After stirring at 30-40°C for 30 min, the mixture was re-cooled to 0°C, and a solution of Intermediate 5A (5.6 g, 16.86 mmol) in 60 ml of dry THF was added dropwise. The mixture was then stirred overnight while warming up to room temperature. Further portions of sodium hydride (0.1 g, 3.4 mmol) and Intermediate 5A (1.12 g, 3.4 mmol) were added at 0°C, and stirring was continued at room temperature for another 3 h. The reaction mixture was quenched by addition of saturated ammonium chloride solution (100 ml) and brine (200 ml), and extracted twice with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and evaporated. The crude product was finally purified by column chromatography using a dichloro-methane / ethyl acetate gradient (50:1 - > 30:1).

20

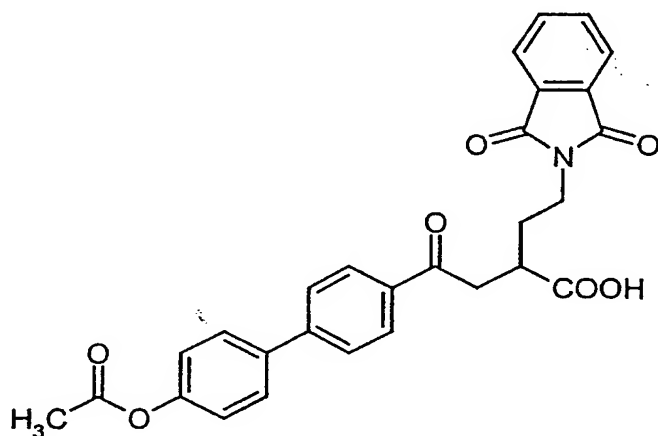
Yield: 4.41 g (41.2%) of an off-white solid.

$^1\text{H-NMR}$ (DMSO-d_6): $\delta = 1.38$ (s, 18 H), 2.32 (m, 5 H), 3.61 (tr, 2 H), 3.73 (s, 2 H), 7.28 (d, 2 H), 7.81 (m, 8 H), 8.04 (d, 2 H).

Example 5

5

(rac)-4-[4'-(Acetyloxy)[1,1'-biphenyl]-4-yl]-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid



10

Intermediate 5G (400 mg, 0.62 mmol) was dissolved at 0°C in a mixture of dichloromethane (5 ml) and trifluoroacetic acid (5 ml). After stirring at room temperature for 1.5 h, 10 ml of toluene were added, and the reaction mixture was evaporated. The residue was dried under vacuum, then re-dissolved in 20 ml of dioxane, and the solution heated under reflux for 6 h. The mixture was evaporated to dryness, the residue triturated with diethyl ether, filtered, and the remaining solid dried under vacuum to give the final product.

15

Yield: 261 mg (86.2%) of an off-white solid.

20

$^1\text{H-NMR}$ (DMSO-d_6): $\delta = 1.95$ (m, 2 H), 2.31 (s, 3 H), 2.89 (m, 1 H), 3.38 (m, 2 H), 3.72 (tr, 2 H), 7.28 (d, 2 H), 7.84 (m, 8 H), 8.07 (d, 2 H), 12.33 (br s, 1 H).

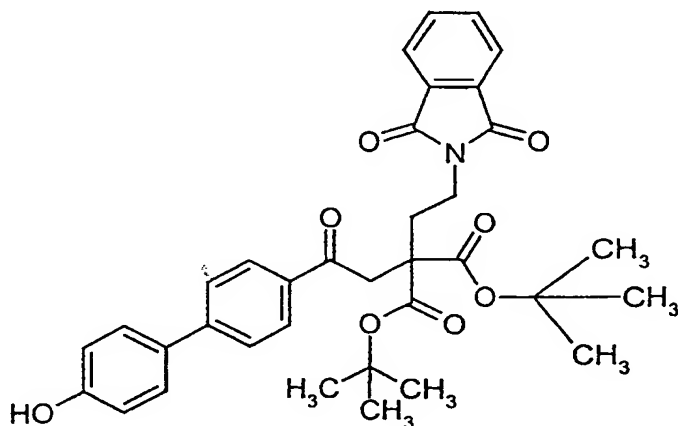
Example 6

(rac)-2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-hydroxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid

5

Intermediate 6A

Di(tert-butyl) 2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-2-[2-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-2-oxoethyl] malonate



10

Finely powdered, anhydrous potassium carbonate (2.15 g, 15.58 mmol) was added to a solution of Intermediate 5G (2.0 g, 3.12 mmol) in 90 ml of a THF / methanol / ethanol mixture (30:50:10). The resulting suspension was vigorously stirred at room temperature for 45 min, then diluted with ethyl acetate and filtered. The filtrate was concentrated under vacuum to half of its original volume, diluted again with ethyl acetate, and then poured into an ice-cold pH 4 buffer solution. The aqueous phase was extracted twice with ethyl acetate, and the combined organic layers were dried over Na₂SO₄, filtered and evaporated. After drying under vacuum, 700 mg (approx. 1.1 mmol) of the residue (which contained some ring-opened material) were dissolved in 20 ml of dichloromethane, and 1-hydroxy-1H-benzotriazol hydrate (189 mg, 1.23 mmol) and N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (229 mg, 1.18 mmol) were added at 0°C. The reaction mixture was stirred at room temperature for 3 days, then diluted with dichloromethane, and washed twice

20

with pH 4 buffer solution and with saturated sodium hydrogencarbonate solution. The organic phase was dried over Na₂SO₄, filtered and evaporated. The crude product was finally purified by column chromatography using a dichloromethane / methanol gradient (100:1 -> 80:1).

5

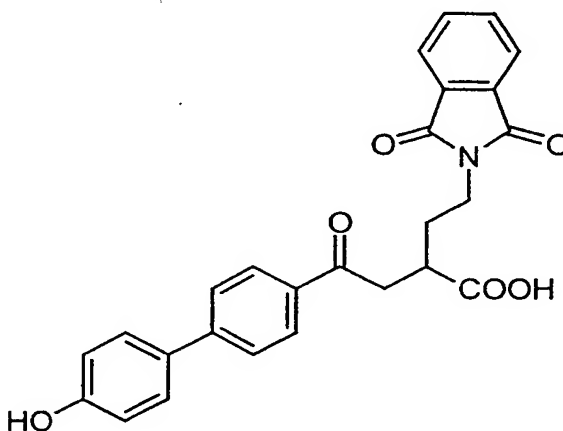
Yield: 494 mg (71%) of a white solid.

¹H-NMR (DMSO-d₆): δ = 1.38 (s, 18 H), 2.31 (m, 2 H), 3.60 (m, 2 H), 3.70 (s, 2 H), 6.90 (d, 2 H), 7.61 (d, 2 H), 7.78 (m, 6 H), 8.00 (d, 2 H), 9.76 (s, 1 H).

10

Example 6

(rac)-2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-hydroxy[1,1'-biphen-yl]-4-yl)-4-oxobutanoic acid



15

Intermediate 6A (490 mg, 0.82 mmol) was dissolved at 0°C in a mixture of dichloromethane (7.5 ml) and trifluoroacetic acid (7.5 ml). After stirring at room temperature for 30 min, 7 ml of toluene were added, and the reaction mixture was evaporated. The residue was dried under vacuum, then re-dissolved in 15 ml of dioxane, and the solution heated under reflux for 4.5 h. After cooling to room temperature, diethyl ether (15 ml) was added to the reaction mixture, and the precipitated product collected by filtration. The filtrate was evaporated to dryness, the residue triturated

20

with diethyl ether, containing a few drops of methanol, and filtered again to give a second crop of the final product.

Yield: 299 mg (82.6%) of a white solid.

5

¹H-NMR (DMSO-d₆): δ = 1.94 (m, 2 H), 2.87 (m, 1 H), 3.38 (m, 2 H), 3.70 (tr, 2 H), 6.89 (d, 2 H), 7.61 (d, 2 H), 7.75 (d, 2 H), 7.85 (m, 4 H), 8.01 (d, 2 H), 9.76 (br s, 1 H), 12.30 (br s, 1 H).

10

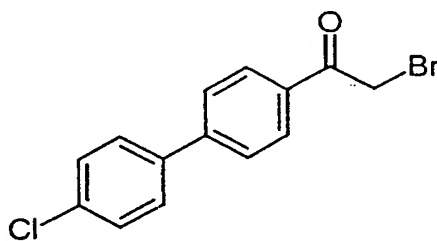
Example 7

(rac)-4-(4'-Chloro[1,1'-biphenyl]-4-yl)-2-[2-(4,6-dimethoxy-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid

15

Intermediate 7A

2-Bromo-1-(4'-chloro[1,1'-biphenyl]-4-yl)-1-ethanone



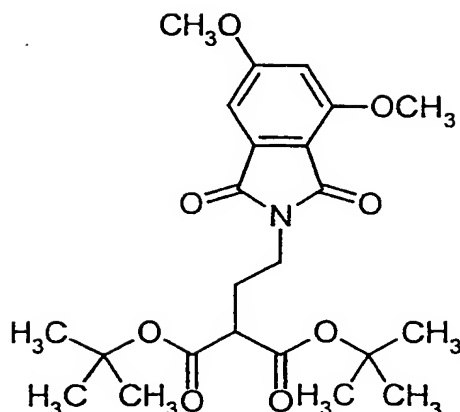
20

This intermediate was prepared as described in the indicated reference WO 96/15096.

Intermediate 7B

25

Di(tert-butyl) 2-[2-(4,6-dimethoxy-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl] malonate



To a stirred solution of Intermediate 5E (8.4 g, 32.2 mmol) in 100 ml of dry THF were added successively 3,5-dimethoxyphthalimide (10.0 g, 48.3 mmol), triphenyl phosphine (11.1 g, 41.8 mmol) and, at 0°C, diethyl azodicarboxylate (6.7 g, 38.6 mmol). The resulting solution was stirred overnight while warming up to room temperature. After filtration, the filtrate was diluted with ethyl acetate and washed twice with water and with brine. The organic phase was dried over Na₂SO₄, filtered and evaporated. The crude product was finally purified by column chromatography using a dichloromethane / ethyl acetate gradient (70:1 -> 30:1).

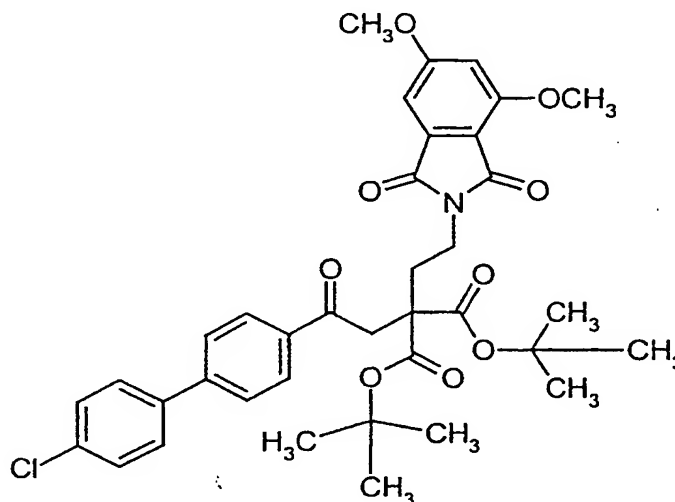
Yield: 2.69 g (18.6%) of a white solid.

¹H-NMR (DMSO-d₆): δ = 1.38 (s, 18 H), 1.97 (q, 2 H), 3.23 (tr, 1 H), 3.54 (tr, 2 H), 3.92 (s, 6 H), 6.89 (d, 1 H), 6.97 (d, 1 H).

Intermediate 7C

Di(tert-butyl) 2-[2-(4'-chloro[1,1'-biphenyl]-4-yl)-2-oxoethyl]-2-[2-(4,6-dimethoxy-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl] malonate

5



Under argon, a solution of Intermediate 7B (2.69 g, 5.98 mmol) in 30 ml of dry THF was added dropwise at 0°C to a suspension of sodium hydride (0.18 g, 80% suspension in mineral oil, 6.04 mmol) in 20 ml of dry THF. After stirring at 30–40°C for 30 min, the mixture was re-cooled to 0°C, and a solution of Intermediate 3A (1.87 g, 6.04 mmol) in 20 ml of dry THF was added dropwise. The mixture was then stirred overnight while warming up to room temperature. Further portions of sodium hydride (36 mg, 1.2 mmol) and Intermediate 7A (374 mg, 1.2 mmol) were added at 0°C, and stirring was continued at room temperature for three days. The reaction mixture was quenched by addition of saturated ammonium chloride solution (40 ml) and brine (80 ml), and extracted twice with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and evaporated. The crude product was finally purified by column chromatography using a dichloro-methane to dichloromethane / ethyl acetate (20:1) gradient.

20

Yield: 1.51 g (37.2%) of a white solid.

- 76 -

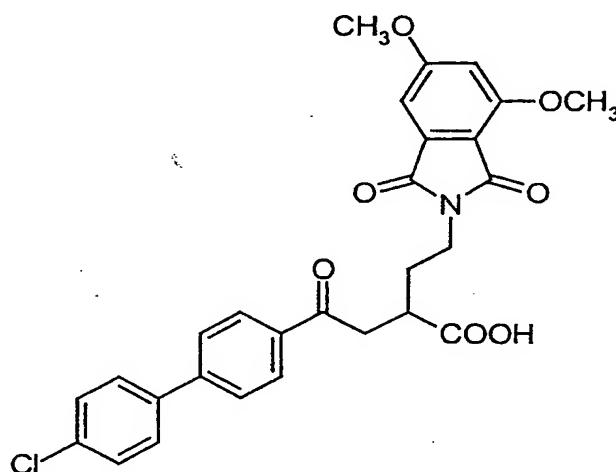
$R_F = 0.51$ (dichloromethane / ethyl acetate 20:1)

$= 0.59$ (cyclohexane / ethyl acetate 1:1)

- 5 ESI-MS: $m/z = 678$ $[M+H]^+$, 622 $([M+H]^+ - C_4H_8)$, 566 $([M+H]^+ - 2 \times C_4H_8)$, 548 $([M+H]^+ - 2 \times C_4H_8 - H_2O)$.

Example 7

- 10 *(rac)*-4-(4'-Chloro[1,1'-biphenyl]-4-yl)-2-[2-(4,6-dimethoxy-1,3-dioxo-1,3-dihydro-2H-isindol-2-yl)ethyl]-4-oxobutanoic acid



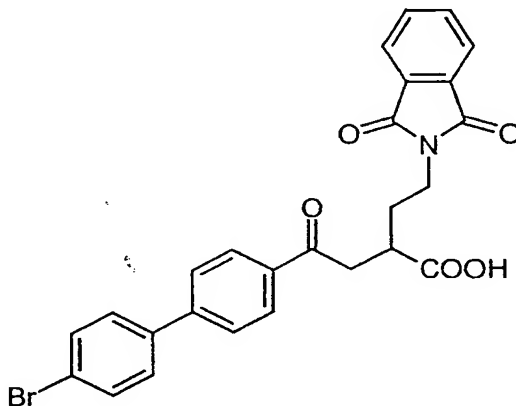
- 15 Intermediate 7C (1.5 g, 2.2 mmol) was dissolved at 0°C in a mixture of dichloromethane (10 ml) and trifluoroacetic acid (10 ml). After stirring at room temperature for 45 min, 10 ml of toluene were added, and the reaction mixture was evaporated. The residue was dried under vacuum, then re-dissolved in 20 ml of dioxane, and the solution heated under reflux for 6 h. The mixture was evaporated to dryness, the residue triturated with diethyl ether, filtered, and the remaining solid
- 20 dried under vacuum to give the final product.

Yield: 1.07 g (92.1%) of an off-white solid.

¹H-NMR (DMSO-d₆): δ = 1.89 (m, 2 H), 2.84 (m, 1 H), 3.39 (m, 2 H), 3.63 (tr, 2 H), 3.92 (s, 6 H), 6.88 (d, 1 H), 6.97 (d, 1 H), 7.58 (d, 2 H), 7.82 (m, 4 H), 8.07 (d, 2 H), 12.30 (br s, 1 H).

5 Examples 8 and 9

(+)- and (-)-4-(4'-Bromo[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid



Racemic 4-(4'-Bromo[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)- ethyl]-4-oxobutanoic acid was prepared essentially as described in the indicated reference WO 96/15096.

¹H-NMR (DMSO-d₆): δ = 1.95 (m, 2 H), 2.88 (m, 1 H), 3.38 (m, 2 H), 3.72 (tr, 2 H), 7.72 (m, 4 H), 7.85 (m, 6 H), 8.08 (d, 2 H), 12.33 (br s, 1 H).

1.0 g (1.97 mmol) of this material was separated into pure enantiomers by chiral HPLC using a commercially available 5 μm Kromasil KR 100-5-CHI-DMB phase. A solvent mixture consisting of 40% iso-hexane and 60% of a tert-butylmethyl ether / dichloromethane / glacial acetic acid mixture (480:40:1) was employed at a constant flow rate of 25 ml/min.

Example 8

First eluting enantiomer A:

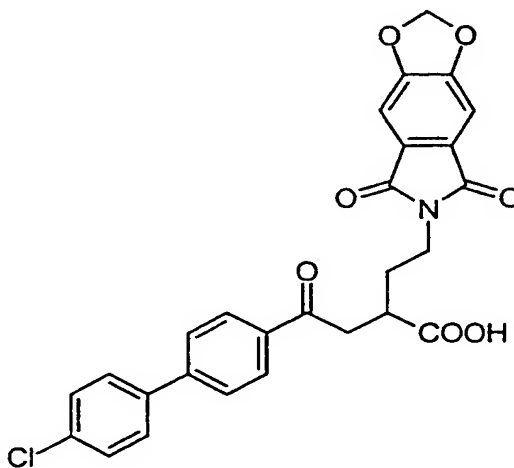
5 Yield: 309 mg (31%)

 $[\alpha]_D^{20} = +3.87^\circ$ (c = 0.458 g / 100 ml, THF)**Example 9**

10

Second eluting enantiomer B:

Yield: 240 mg (24%)

15 $[\alpha]_D^{20} = -5.98^\circ$ (c = 0.482 g / 100 ml, THF)**Examples 10 and 11**20 *(+)- and (-)-4-(4'-Chloro[1,1'-biphenyl]-4-yl)-2-[2-(5,7-dioxo-5,7-dihydro-6H-[1,3]-dioxolo[4,5-f]isoindol-6-yl)ethyl]-4-oxobutanoic acid*

Racemic 4-(4'-Chloro[1,1'-biphenyl]-4-yl)-2-[2-(5,7-dioxo-5,7-dihydro-6H-[1,3]-dioxolo-[4,5-f]isoindol-6-yl)ethyl]-4-oxobutanoic acid was prepared essentially as described in the indicated reference WO 96/15096.

5 $^1\text{H-NMR}$ (DMSO-d_6): $\delta = 1.91$ (m, 2 H), 2.85 (m, 1 H), 3.38 (m, 2 H), 3.66 (tr, 2 H), 6.26 (s, 2 H), 7.39 (s, 2 H), 7.58 (d, 2 H), 7.82 (m, 4 H), 8.06 (d, 2 H), 12.31 (br s, 1 H).

10 0.70 g (1.38 mmol) of this material was separated into pure enantiomers by chiral HPLC using a commercially available 5 μm Kromasil KR 100-5-CHI-MDB phase. A solvent mixture consisting of 40% iso-hexane and 60% of a tert-butylmethyl ether / dichloromethane / glacial acetic acid mixture (480:40:1) was employed at a constant flow rate of 25 ml/min.

15 **Example 10**

First eluting enantiomer A:

Yield: 261 mg (37.3%)

20

$[\alpha]_{\text{D}}^{20} = +13.99^\circ$ ($c = 0.955$ g / 100 ml, THF)

Example 11

25 Second eluting enantiomer B:

Yield: 228 mg (32.6%)

$[\alpha]_{\text{D}}^{20} = -15.15^\circ$ ($c = 0.991$ g / 100 ml, THF)

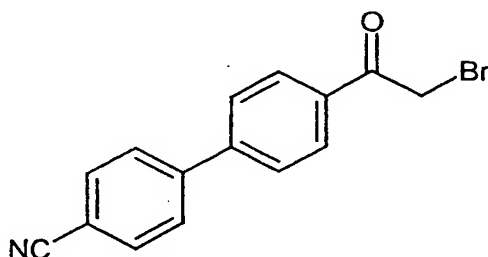
30

Example 12

(rac)-4-(4'-Cyano[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid

5 **Intermediate 12A**

4'-(2-bromoacetyl)[1,1'-biphenyl]-4-carbonitrile



10

4.68 g aluminium chloride (35.15 mmol) are dissolved in 45 ml dichloromethane and treated dropwise with 3.38 g (16.74 mmol) bromoacetyl bromide at 0°C. After 30 min 3 g (16.74 mmol) 4-cyanobiphenyl, dissolved in 15 ml dichloromethane, are added dropwise. The reaction mixture is stirred overnight at ambient temperature, added to ice-water and extracted 2 times with dichloromethane. The organic phase is washed with water and brine, dried and evaporated. The residue is triturated with petrol ether, filtered and dried. Yield: 4.24 g (83%).

15

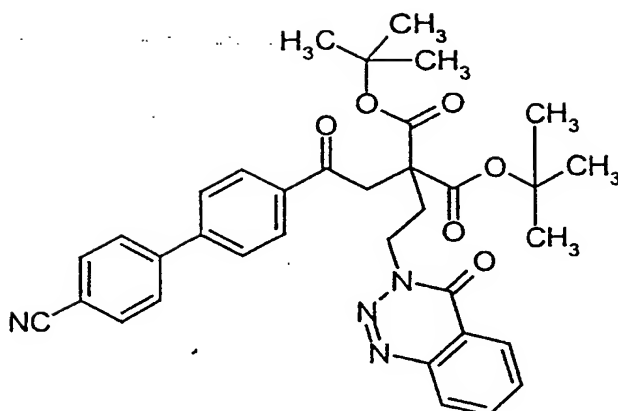
200 MHz ¹H-NMR (CDCl₃): 4.49, s, 2H; 7.73, m, 6H; 8.11, d, 2H.

20

Intermediate 12B

Di(tert-butyl)-2-[2-(4'-cyano[1,1'-biphenyl]-4-yl)-2-oxoethyl]-2-{2-[4-oxo-1,2,3-benzo-triazin-3(4H)-yl]ethyl}malonate

25



A solution of 2.59 g (6.67 mmol) of Intermediate 13C in 20 ml DMF is added dropwise to a suspension of 0.333 g NaH (60% in mineral oil) in 20 ml DMF. The mixture is stirred for 30 min and a solution of 2 g (6.67 mmol) of Intermediate 12A in 20 ml DMF is added. The mixture is stirred for 2.5h at RT, poured onto 150 ml NH₄Cl solution and extracted with ethyl acetate. The organic phase is washed with water and brine, dried over MgSO₄ and evaporated. The residue is purified by chromatography to give 0.62 g (15%).

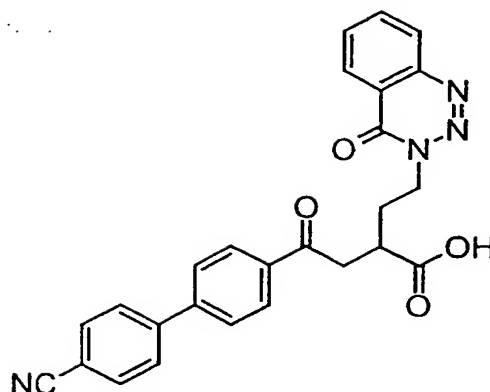
10

200 MHz ¹H-NMR (CDCl₃): 2.71, s, 2H; 3.81, s, 2H; 4.53, m, 2H; 7.75, m, 7H; 7.91, m, 1H; 8.10, m, 3H; 8.30, m, 1H.

Example 12

15

(rac)-4-(4'-Cyano[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid

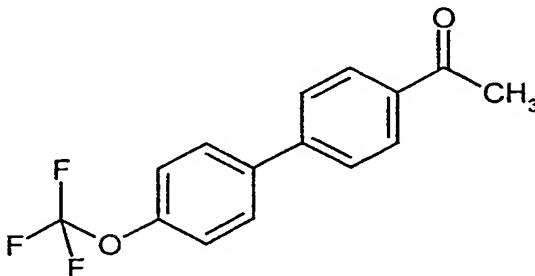


0.61 g (1 mmol) of Intermediate 12B is dissolved in 10 ml dichloro-methane / trifluoroacetic acid (1:1) at 0°C and the mixture is stirred for 2h at RT. After adding
5 toluene the reaction mixture is evaporated to dryness and the residue taken into 10 ml dioxane. The solution is stirred under reflux for 6h and at RT overnight. The solvent is removed in vacuo and the residue purified by HPLC to yield 96 mg (21%).

200 MHz ¹H-NMR (CDCl₃): 2.28, m, 2H; 2.49, m, 2H; 3.26, m, 1H; 4.58, m, 2H,
10 7.72, m, 10H; 8.18, m, 1H; 8.38, m, 1H.

Example 13

(rac)-4-Oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}-4-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]butanoic acid
15

Intermediate 13A*1-[4'-(Trifluoromethoxy)[1,1'-biphenyl]-4-yl]-1-ethanone*

5

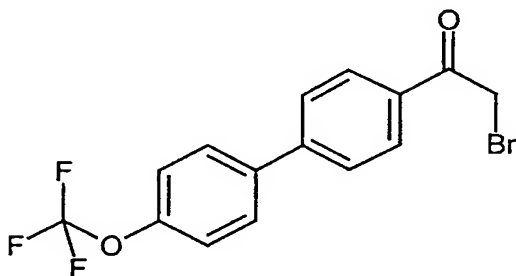
To a mixture of 30 g (126 mmol) 4-(trifluoromethoxy)-1,1'-biphenyl and 21 g aluminium trichloride (157 mmol) in 120 ml nitrobenzene are added at a temperature below 20°C 9.87 g (126 mmol) acetyl chloride. The reaction mixture is stirred for 2h
10 at 0°C, added to 240 ml ice-water and 42 ml conc. HCl and extracted with ethyl acetate. The organic phase is washed with water and brine and the solvents removed in vacuo. The residue is triturated with petrol ether, filtrated and dried. From the filtrate another batch can be obtained after crystallizing at 4°C to give overall 23.5 g (66%).

15

200 MHz ¹H-NMR (CDCl₃): 2.65, s, 3H; 7.33, d, 2H; 7.58, m, 4H; 8.06, d, 2H.

Intermediate 13B

2-Bromo-1-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]-1-ethanone



5

12.27 g (43.8 mmol) of Intermediate 13A are dissolved in a mixture of 150 ml methanol, 150 ml ethanol and 50 ml ether with gentle heating. 5.914 g (56.9 mmol) boronic acid trimethylester are added at RT and 7.35 g (45.9 mmol) bromine are added dropwise. The reaction mixture is stirred until disappearance of the red-brown colour. Solvents are removed in vacuo and the residue is purified by chromatography (cyclohexane/ethyl acetate) to give 6.2 g (39%).

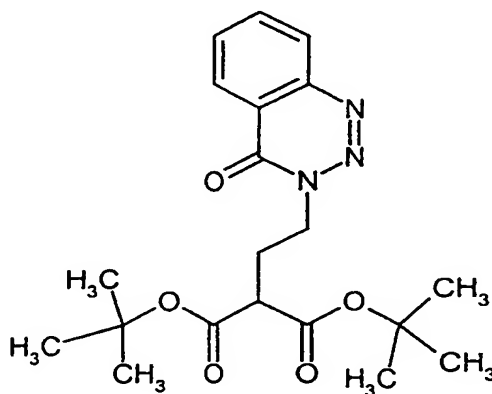
10

200 MHz ¹H-NMR (CDCl₃): 4.49, s, 2H; 7.33, d, 2H; 7.68, dd, 4H; 8.10, d, 2H.

15

Intermediate 13C

Di(tert-butyl) 2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}malonate



20

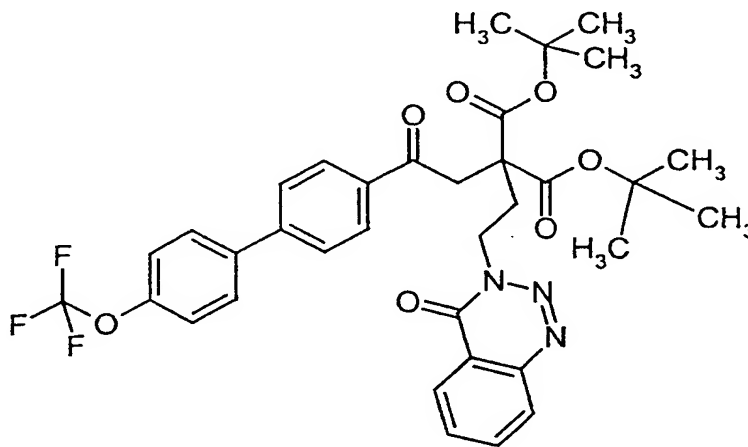
46.2 g (177 mmol) of Intermediate 5E are dissolved in 600 ml THF. 69.8 g (266 mmol) triphenylphosphine and 39.2 g (266 mmol) 1,2,3-benzotriazin-4(3H)-one are added. 46.4 g (266 mmol) DEAD are added dropwise. The reaction mixture was stirred overnight at room temperature. The solvent is removed in vacuo and the product obtained by chromatography (cyclohexane/ethylacetate 6:1).

Yield: 51.8 g (63%).

200 MHz ^1H -NMR (CDCl_3): 1.43, s, 18H; 2.43, quar., 2H; 3.30, t, 1H; 4.57, t, 2H; 7.80, m, 1H; 7.94, m, 1H; 8.16, dd, 1H; 8.36, dd, 1H.

Intermediate 13D

Di(tert-butyl)-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}-2-{2-oxo-2-[4'-(trifluoromethoxy)[1,1'-biphenyl]-4-yl]ethyl}malonate



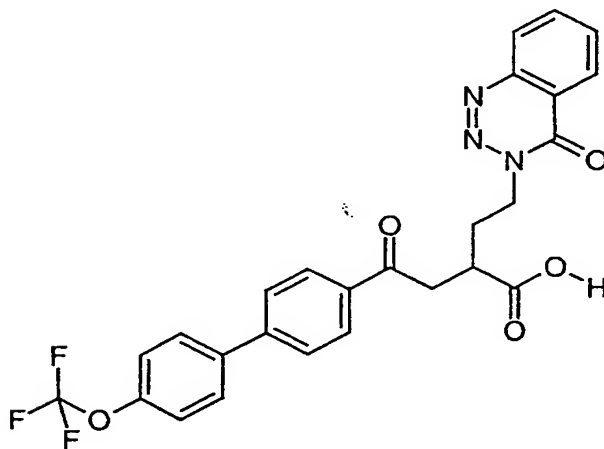
To a suspension of 0.52 g (12.9 mmol) sodium hydride (60% suspension in mineral oil) in 20 ml DMF is added a solution of 4.04 g (10.37 mmol) of Intermediate 13C in 30 ml DMF dropwise. After stirring for 30 min at RT a solution of 3.73 g (10.37 mmol) of Intermediate 13B in 30 ml DMF is added dropwise and the reaction mixture is stirred for 2h at RT. The reaction mixture is poured onto NH_4Cl solution, extracted with ethyl acetate and the organic phase is washed with water and brine.

After drying and evaporation of the solvents the product is purified by chromatography to give 2.09 g (30%).

200 MHz ^1H -NMR (CDCl_3): 2.70, m, 2H; 3.82, s, 2H; 4.54, m, 2H; 7.32, d, 2H;
5 7.62, m, 5H; 8.07, m, 4H; 8.30, m, 1H.

Example 13

(rac)-4-Oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}-4-[4'-(trifluoro-meth-
10 oxy)[1,1'-biphenyl]-4-yl]butanoic acid

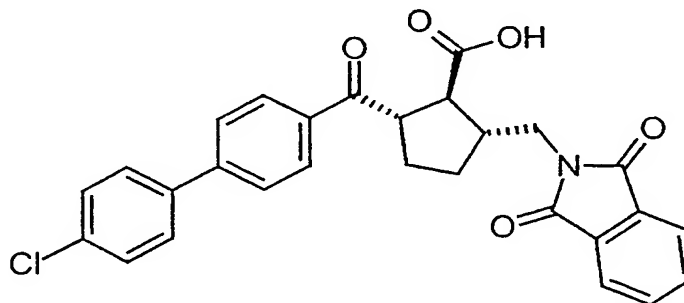


A solution of 2.09 g (3.13 mmol) of Intermediate 13C in 15 ml dichloromethane and
15 15 ml trifluoroacetic acid is stirred at RT for 2h. After adding toluene the solvents
are removed in vacuo. The residue is dissolved in 30 ml dioxane, the solution is
refluxed for 6h and stirred at RT overnight. Solvents are removed in vacuo, the
residue is triturated with ether, the precipitate is collected by filtration and dried to
give 0.51 g (32%).

20 200 MHz ^1H -NMR ($\text{DMSO}-d_6$): 2.18, m, 2H; 2.98, m, 1H; 3.51, m, 2H; 4.52, m, 2H;
7.52, d, 2H; 7.89, m, 5H; 8.10, m, 3H; 8.24, m, 2H; 12.39, s, 1H.

Example 14 and 15

(+)- and (-)-(1*S*, 2*S*, 5*R*)-2-[(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]-5-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]cyclopentanecarboxylic acid



5

The racemic compound was prepared essentially following the procedure for Example 360 of WO 96/15096.

10 4.20 g (8.61 mmol) of this material was separated into pure enantiomers by chiral HPLC using a commercially available 5 μ m Kromasil KR 100-5-CHI-MDB phase. A solvent mixture consisting of 30% iso-hexane and 70% of a tert-butylmethyl ether /dichloromethane/glacial acetic acid mixture (480:40:1) was employed at a constant flow rate of 25 ml/min.

15

Example 14

First eluting enantiomer A:

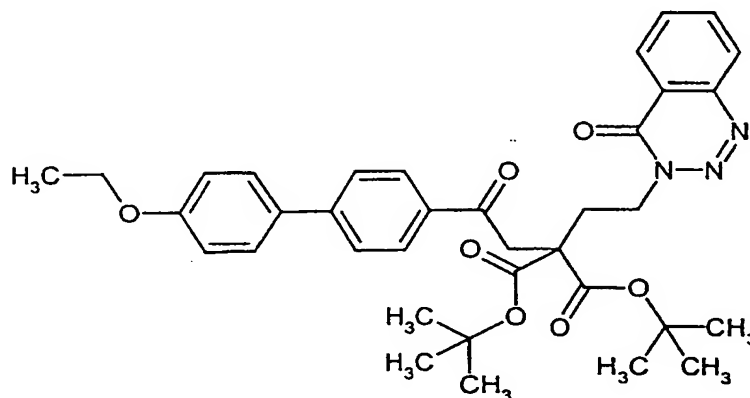
Yield: 1.72 g (41.0%)

20 $[\alpha]_D^{21} = +44.26^\circ$ (c=0.464 g/100 ml, THF)

Example 15

Second eluting enantiomer B:

Yield: 1.59 g (37.9%)

5 $[\alpha]_D^{21} = 43.70^\circ$ (c = 0.575 g/100 ml, THF)**Example 16**10 *(rac)-4-(4'-Ethoxy-biphenyl-4-yl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-4-oxo-butyric acid***Intermediate 16 A**15 *tert.-Butyl-4-(4'-ethoxy-biphenyl-4-yl)-4-oxo-2-(tert.-butoxycarbonyl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-butanoate*20 A solution of Intermediate 13C (1.29 g, 3.32 mmol) in 15 mL DMF was added dropwise to a suspension of NaH (170 mg, 4.15 mmol) in 5 mL DMF and stirred for 30 min at rt. Intermediate 1B (1.06 g, 3.32 mmol) in 15 ml DMF was added slowly and the resulting mixture was stirred for 2.5 h at rt. The reaction was quenched with saturated NH₄Cl solution, extracted twice with diethyl ether, washed with saturated

NaHCO₃, water and brine, dried (Na₂SO₄) and evaporated. The crude product was purified using flash chromatography (Hexane / Ethyl acetate : 9/1 → 5/1).

Yield: 1.34 g (59 %)

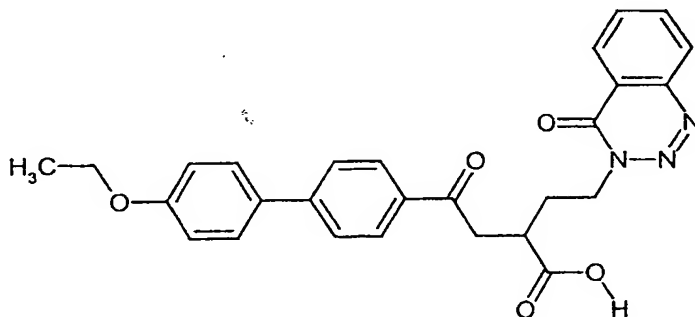
5

¹H-NMR (D₆-DMSO): 7.65-8.25 (m, 10H), 7.05 (d, J=8Hz, 2H), 4.39-4.51 (m, 2H), 4.1 (q, J=7Hz, 2H), 3.75 (s, 2H), 2.45-2.55 (m, 2H), 1.33-1.4 (m, 21H)

Example 16

10

(rac)-4-(4'-Ethoxy-biphenyl-4-yl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-4-oxo-butyric acid



15 1.31 g (2.09 mmol) of Intermediate 16A were added in one portion to a cooled (0°C) 1:1 mixture of CH₂Cl₂ and trifluoroacetic acid (20 mL). The reaction mixture was stirred for 2 h at rt, evaporated and dried under vacuum. The residue was dissolved in 20 mL dioxane and heated for 5 h under reflux. The reaction mixture was evaporated, the residue triturated with ethylacetate, stirred for 15 min and filtered. The remaining
20 solid was dried under vacuum.

Yield: 0.77 g (78 %)

¹H-NMR (DMSO-d₆): 12.35 (s, 1H), 8.18-8.3 (m, 2H), 7.9-8.15 (m, 4H), 7.79 (d, J=8Hz, 2H), 7.61 (d, J=8Hz, 2H), 7.05 (d, J=8Hz, 2H), 4.42-4.65 (m, 2H), 4.1 (q,

25

J=7Hz, 2H), 3.24-3.6 (m, 4H), 2.88-3.05 (m, 1H), 2.02-2.35 (m, 2H), 1.38 (t, J=7Hz, 3H)

5 The compound of Example 16 was separated into its pure enantiomers by HPLC on a Kromasil 100-5-CHI-DMB (5 μ m) column using a mixture consisting of n-heptane : (0.2% acetic acid/TBME) : dichloromethane (40 : 54 : 6 by volume) as eluant.

Example 17

10 (+)-4-(4'-Ethoxy-biphenyl-4-yl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-4-oxo-butyric acid

First eluting enantiomer A

Yield: 168 mg (24 %)

15 $[\alpha]_D^{20}$ (c= 0.66g/100ml, THF) = +17.05°

Example 18

20 (-)-4-(4'-Ethoxy-biphenyl-4-yl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-4-oxo-butyric acid

Second eluting enantiomer B:

Yield: 153 mg (22%)

25 $[\alpha]_D^{20}$ (c= 0.58g/100ml, THF) = -18.78°

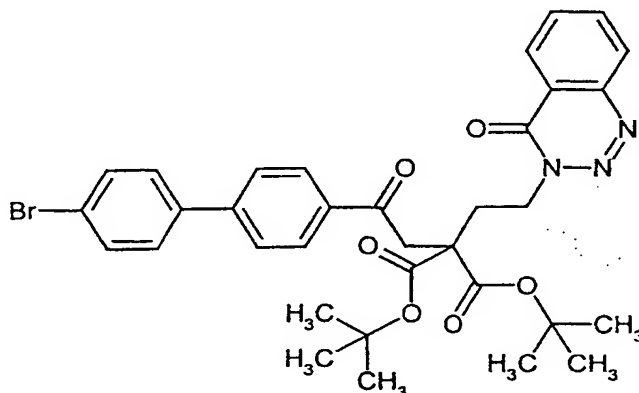
Example 19

30 4-(4'-Bromo-biphenyl-4-yl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-4-oxo-butyric acid

Intermediate 19A

tert.-Butyl-4-(4'-bromo-biphenyl-4-yl)-4-oxo-2-(tert.-butyloxycarbonyl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-butanoate

5



A solution of Intermediate 13C (1.27 g, 3.25 mmol) in 15 mL DMF was added dropwise to a suspension of NaH (160 mg, 4.06 mmol) in 5 mL DMF and stirred for 30 min at rt. 2-Bromo-4'-(4'-bromo-phenyl) acetophenone (1.15 g, 3.25 mmol) in 15 ml DMF was added slowly and the resulting mixture was stirred for 2.5 h at rt. The reaction was quenched with saturated NH₄Cl solution, extracted twice with diethyl ether, washed with saturated NaHCO₃, water and brine, dried (Na₂SO₄) and evaporated. The crude product was purified using flash chromatography (Hexane / Ethyl acetate : 9/1-> 3/1).

15

Yield: 1.27 g (58 %)

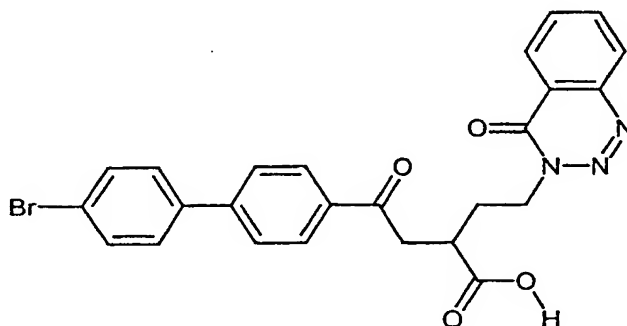
¹H-NMR (DMSO-d₆): 7.88-8.25 (m, 6H), 7.81 (d, J=8Hz, 2H), 7.7 (s, 4H), 4.39-4.51 (m, 2H), 3.75 (s, 2H), 2.45-2.58 (m, 2H), 1.4 (s, 18H)

20

Example 19

(rac)-4-(4'-Bromo-biphenyl-4-yl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-4-oxo-butyric acid

5



1.24 g (1.87 mmol) of Intermediate 19A was added in one portion to a cooled (0°C) 1:1 mixture of CH₂Cl₂ and trifluoroacetic acid (20 mL). The reaction mixture was stirred for 2 h at rt, evaporated and dried under vacuum. The residue was dissolved in 20 mL dioxane and heated for 5 h under reflux. The reaction mixture was evaporated, the residue triturated with ethylacetate, stirred for 15 min and filtered. The remaining solid was dried under vacuum.

Yield: 0.77 g (78 %)

¹H-NMR (DMSO-d₆): 12.4 (s, 1H), 7.9-8.3 (m, 6H), 8.579 (d, J=8Hz, 2H), 7.72 (s, 4H), 3.28-3.62 (m, 4H), 2.88-3.05 (m, 1H), 2.02-2.35 (m, 2H)

700 mg of the compound of Example 19 were separated into the pure enantiomers by HPLC on a Kromasil 100-5-CHI-DMB (5µm) column using a mixture consisting of n-heptane : (0.2% acetic acid/TBME) : dichloromethane (40 : 54 : 6 by volume) as eluant.

Example 20

(+)-4-(4'-Bromo-biphenyl-4-yl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-4-oxo-butyric acid

5

First eluting enantiomer A:

Yield: 265mg (38%)

$[\alpha]_D^{20}$ (c=0.61g/100ml, THF) = +14.34°

10

Example 21

(-)-4-(4'-Bromo-biphenyl-4-yl)-2-[2-(4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-ethyl]-4-oxo-butyric acid

15

Slower eluting enantiomer B:

Yield: 219mg (31%)

$[\alpha]_D^{20}$ (c=0.62 g/100ml, THF) = -14.32°

Example 22

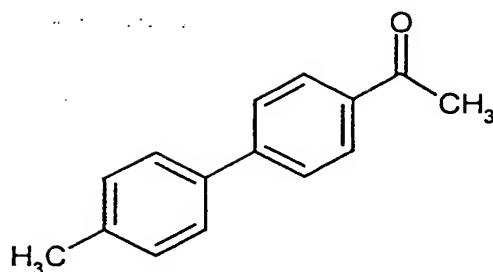
20

(rac)-4-(4'-methyl[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid

Intermediate 22A

25

1-(4'-methyl[1,1'-biphenyl]-4-yl)-1-ethanone



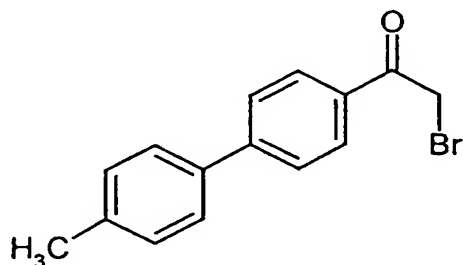
20 g (119 mmol) 4-methylbiphenyl and 19.81 g (149 mmol) aluminiumchloride are dissolved in 120 ml dichloromethane. At a temperature below 20°C 9.38 g
5 (119 mmol) acetylchloride is added dropwise and the reactionmixture is stirred at roomtemperature for 2hrs. The solution is added to a mixture of 200 ml ice water and 55 ml conc. HCl, the organic phase is separated, dried and concentrated. The residue was purified by chromatography (cyclohexane/ethylacetate=10:1).

10 Yield: 11.5g (46%).

200 MHz ¹H-NMR (CDCl₃): 2.41, s, 3H; 2.62, s, 3H; 7.29, d, 2H; 7.53, d, 2H; 7.68, d, 2H; 8.02, d, 2H.

15 **Intermediate 22B**

2-bromo-1-(4'-methyl[1,1'-biphenyl]-4-yl)-1-ethanone



20

4.76 g (22.6 mmol) of Intermediate 22A are dissolved in a mixture of 50 ml ether and 50 ml methanol with gentle heating. The solution is treated with 3.06 g (29.4 mmol)

boronic acid trimethylester at room temperature. 4.16 g (26 mmol) bromine are added dropwise at 0°C. The reaction mixture is stirred until disappearance of the yellow colour. The solvents are removed in vacuo and the product obtained by triturating with ether.

5

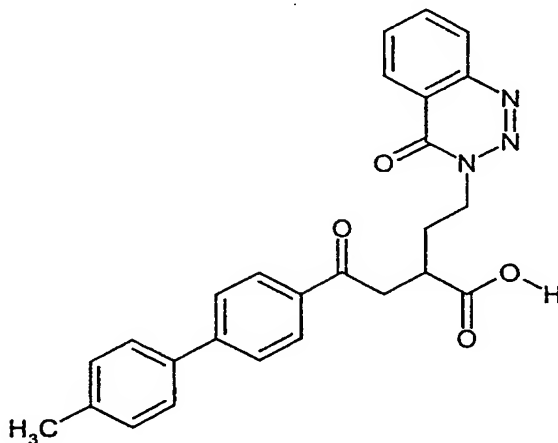
Yield: 4.69 g (72%)

200 MHz ¹H-NMR (CDCl₃): 2.41, s, 3H; 4.47, s, 2H; 7.29, d, 2H; 7.53, d, 2H; 7.70, d, 2H; 8.06, d, 2H.

10

Example 21

(rac)-4-(4'-methyl[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid



15

To a suspension of 0.257 g (6.42 mmol) sodium hydride (60% in mineral oil) in 20 ml DMF under argon is added dropwise a solution of 2.0 g (5.14 mmol) of Intermediate 13C in 20 ml DMF. After stirring for 30 minutes at room temperature 1.49 g (5.14 mmol) Intermediate 21B in 20 ml DMF are added dropwise. The reaction mixture is stirred at room temperature for 2.5 hrs and poured onto 150 ml saturated NH₄Cl-solution. The aqueous phase is extracted twice with ethylacetate, the combined organic phases are dried and solvents removed in vacuo. The residue is

20

purified by chromatography (cyclohexan/ethylacetate:10:1), to give 1.87 g (61%) di(tert-butyl)2-[2-(4'-methyl[1,1'-biphenyl]-4-yl)-2-oxoethyl]-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}malonate.

5 0.46 g (0.77 mmol) di(tert-butyl)2-[2-(4'-methyl[1,1'-biphenyl]-4-yl)-2-oxoethyl]-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}malonate is dissolved in a mixture of 4ml dichloromethane and 4ml trifluoroacetic acid and the resulting solution is stirred for 2 hrs at room temperature. 10ml toluene are added and the solvents are removed in vacuo. The residue is taken up in 8ml 1,4-dioxane and the resulting solution re-
10 fluxed for 6 hrs and stirred at room temperature for 12hrs. The solvent is removed in vacuo and the product obtained by trituration with ethylacetate.

yield: 0.233g (65%)

15 200 MHz ¹H-NMR (CDCl₃+DMSO): 2.22, m, 1H; 2.40, s, 3H; 2.70-3.02, m, 2H; 3.29, m, 1H; 3.54, m, 1H; 4.63, t, 2H; 7.28, d, 2H; 7.55, d, 2H; 7.65, d, 2H; 7.78-8.04, m, 4H; 8.16, d, 1H; 8.33, d, 1H.

The compound of Example 22 was separated into its pure enantiomers by HPLC on a
20 Kromasil 100-5-CHI-DMB (5µm) column using a mixture consisting of i-heptane : dichloromethane : acetic acid (480 : 40 : 1 by volume) as eluant.

Example 23

25 *(+)-4-(4'-methyl[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid*

First eluting enantiomer A:

$[\alpha]_D^{20}(c=0.88 \text{ g/100ml, THF}) = +15.2^\circ$

Example 24

(-)-4-(4'-methyl[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid

5

Second eluting enantiomer B

$[\alpha]_D^{20}$ (c=0.93 g/100ml, THF) = -13.2°

Example 25

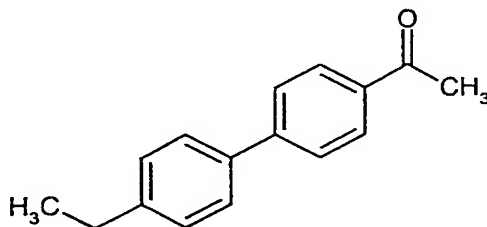
10

(rac)-4-(4'-ethyl[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid

Intermediate 25A

15

1-(4'-ethyl[1,1'-biphenyl]-4-yl)-1-ethanone



- 20 10 g (55 mmol) 4-ethylbiphenyl and 9.15 g (169 mmol) aluminiumtrichloride are dissolved in 60 ml nitrobenzene. At a temperature below 20°C 4.31 g (55 mmol) acetylchloride is added dropwise and the reaction mixture is stirred at room temperature for 2 hrs. The solution is added to a mixture of 80 ml ice water and 14 ml conc. HCl, the organic phase is separated, dried and concentrated. The product
- 25 is obtained by trituration with petrolether.

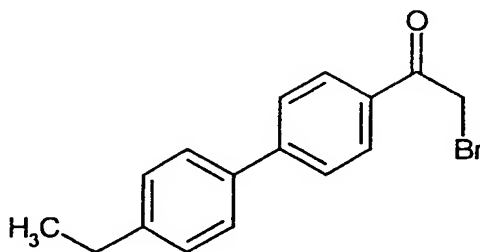
Yield: 8.8g (71%):

200 MHz ^1H -NMR (CDCl_3): 1.29, t, 3H; 2.52, s, 3H; 2.72, quart., 2H; 7.30, d, 2H; 7.58, d, 2H; 7.69, d, 2H; 8.02, d, 2H.

5

Intermediate 25B

2-bromo-1-(4'-ethyl[1,1'-biphenyl]-4-yl)-1-ethanone



10

3.45 g (15.4 mmol) of Intermediate 25A are dissolved in a mixture of 70 ml methanol and 40 ml ethanol with gentle heating. The solution is treated with 2.08 g (20mmol) boronicacidtrimethylester at roomtemperature. 2.7 g (20 mmol) bromine are added dropwise at 0°C. The reaction mixture is stirred until disappearance of the yellow colour. The solvents are removed in vacuo and the product obtained by tritulating with ether.

15

Yield: 3.74g (76%)

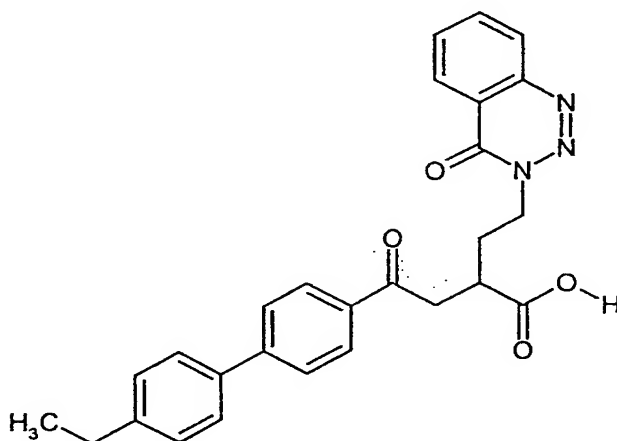
20

200 MHz ^1H -NMR (CDCl_3): 1.29, t, 3H; 2.72, quar., 2H; 4.47, s, 2H; 7.32, d, 2H; 7.57, d, 2H; 7.70, d, 2H; 8.04, d, 2H.

Example 25

(rac)-4-(4'-ethyl[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid

5



To a suspension of 0.330 g (8.25mmol) sodiumhydride (60% in mineral oil) in 20 ml DMF under argon is added dropwise a solution of 2.57g (6.6 mmol) of Intermediate 13C in 20 ml DMF. After stirring for 30 minutes at room temperature 2.0 g (6.60 mmol) of Intermediate 25B in 20 ml DMF are added dropwise. The reaction mixture is stirred at room temperature for 2.5 hrs and poured onto 150 ml saturated NH_4Cl -solution. The aqueous phase is extracted twice with ethylacetate, the combined organic phases are dried and solvents removed in vacuo. The residue is purified by chromatography (cyclohexan/ethylacetate:10:1), to give 3.44 g (85%) di(tert-butyl)2-[2-(4'-ethyl[1,1'-biphenyl]-4-yl)-2-oxoethyl]-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}malonate.

3.44 g (5.62 mmol) di(tert-butyl)2-[2-(4'-ethyl[1,1'-biphenyl]-4-yl)-2-oxoethyl]-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}malonate is dissolved in a mixture of 30 ml dichloromethane and 30 ml trifluoroaceticacid and the resulting solution is stirred for 2 hrs at room temperature. 10 ml toluene are added and the solvents are removed in vacuo. The residue is taken up in 60 ml 1,4-dioxane and the resulting solution re-

fluxed for 6 hrs and stirred at room temperature for 12hrs. The solvent is removed in vacuo and the product obtained by trituration with ethylacetate.

yield: 1.77g (67%)

5 200 MHz ¹H-NMR (DMSO-d₆): 1.22, t, 3H; 2.02-2.33, m, 2H; 2.67, quar., 2H; 2.97, m, 1H; 3.26-3.62, m, 2H; 4.53, t, 2H; 7.35, d, 2H; 7.69, d, 2H; 7.82, d, 2H; 7.89-8.13, m, 4H; 8.23, t, 2H; 12.37, s, 1H.

10 The compound of Example 25 was separated into its pure enantiomers by HPLC in analogy to Example 21.

Example 26

15 *(+)-4-(4'-ethyl[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]ethyl}butanoic acid*

First eluting enantiomer A:

$[\alpha]_D^{20}(c=0.91 \text{ g/100ml, THF}) = +14.4^\circ$

20 Example 27

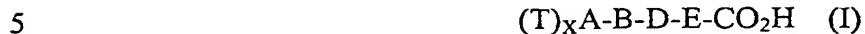
(-)-4-(4'-ethyl[1,1'-biphenyl]-4-yl)-4-oxo-2-{2-[4-oxo-1,2,3-benzotriazin-3(4H)-yl]-ethyl}butanoic acid

25 Second eluting enantiomer B:

$[\alpha]_D^{20}(c=0.91 \text{ g/100ml, THF}) = -16.2^\circ$

Claims

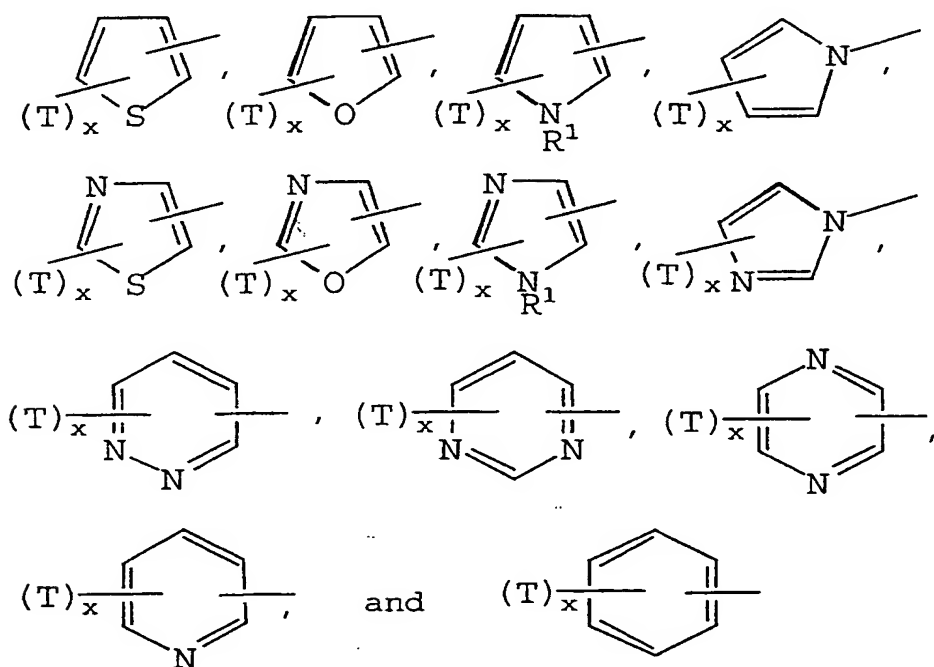
1. Use of compounds of the generalized formula (I):



wherein

(a) $(T)_x A$ represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:

10



wherein R^1 represents H or alkyl of 1 - 3 carbons; and

15 each T represents a substituent group, independently selected from the group consisting of:

- * the halogens -F, -Cl, -Br, and -I;
- * alkyl of 1 - 10 carbons;
- * haloalkyl of 1 - 10 carbons;
- 20 * haloalkoxy of 1 - 10 carbons;

- * alkenyl of 2 - 10 carbons;
- * alkynyl of 2 - 10 carbons;
- * $-(CH_2)_pQ$, wherein
p is 0 or an integer 1 - 4,
- 5 * -alkenyl-Q, wherein
said alkenyl moiety comprises 2 - 4 carbons, and
- * -alkynyl-Q, wherein
said alkynyl moiety comprises 2 - 7 carbons; and

10 Q is selected from the group consisting of aryl of 6 - 10 carbons,
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S
heteroatom, -CN, -CHO, -NO₂, -CO₂R², -OCOR², -SOR³,
-SO₂R³, -CON(R⁴)₂, -SO₂N(R⁴)₂, -C(O)R², -N(R⁴)₂,
-N(R²)COR², -N(R²)CO₂R³, -N(R²)CON(R⁴)₂, -CHN₄, -OR⁴,
15 and -SR⁴;

wherein

R² represents H;

20 alkyl of 1 - 6 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O,
or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons
25 and the alkyl portion contains 1 - 4 carbons; or
heteroaryl-alkyl in which the heteroaryl portion comprises
4 - 9 carbons and at least one N, O, or S heteroatom and
the alkyl portion contains 1 - 4 carbons;

R³ represents alkyl of 1 - 4 carbons;

30 aryl of 6 - 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O,
or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons
and the alkyl portion contains 1 - 4 carbons; or
5 heteroaryl-alkyl in which the heteroaryl portion comprises
4 - 9 carbons and at least one N, O, or S heteroatom and
the alkyl portion contains 1 - 4 carbons;

R⁴ represents H;

alkyl of 1 - 12 carbons;
10 aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O,
or S heteroatom;
arylalkyl in which the aryl portion contains 6 - 10 carbons
and the alkyl portion contains 1 - 4 carbons;
15 heteroaryl-alkyl in which the heteroaryl portion comprises
4 - 9 carbons and at least one N, O, or S heteroatom and
the alkyl portion contains 1 - 4 carbons;

alkenyl of 2 - 12 carbons;
alkynyl of 2 - 12 carbons;
20 $-(C_qH_{2q}O)_rR^5$ wherein q is 1-3; r is 1 - 3; and R⁵ is H
provided q is greater than 1, or alkyl of 1 - 4 carbons, or
phenyl;

alkylenethio terminated with H, alkyl of 1-4 Carbons, or
phenyl;
25 alkyleneamino terminated with H, alkyl of 1-4 carbons, or
phenyl;

$-(CH_2)_sX$ wherein s is 1 - 3 and X is halogen;
 $-C(O)OR^2$; or
 $-C(O)R^2$;

30 and with the provisos that a) when two R⁴ groups are situated
on a nitrogen, they may be joined by a bond to form a

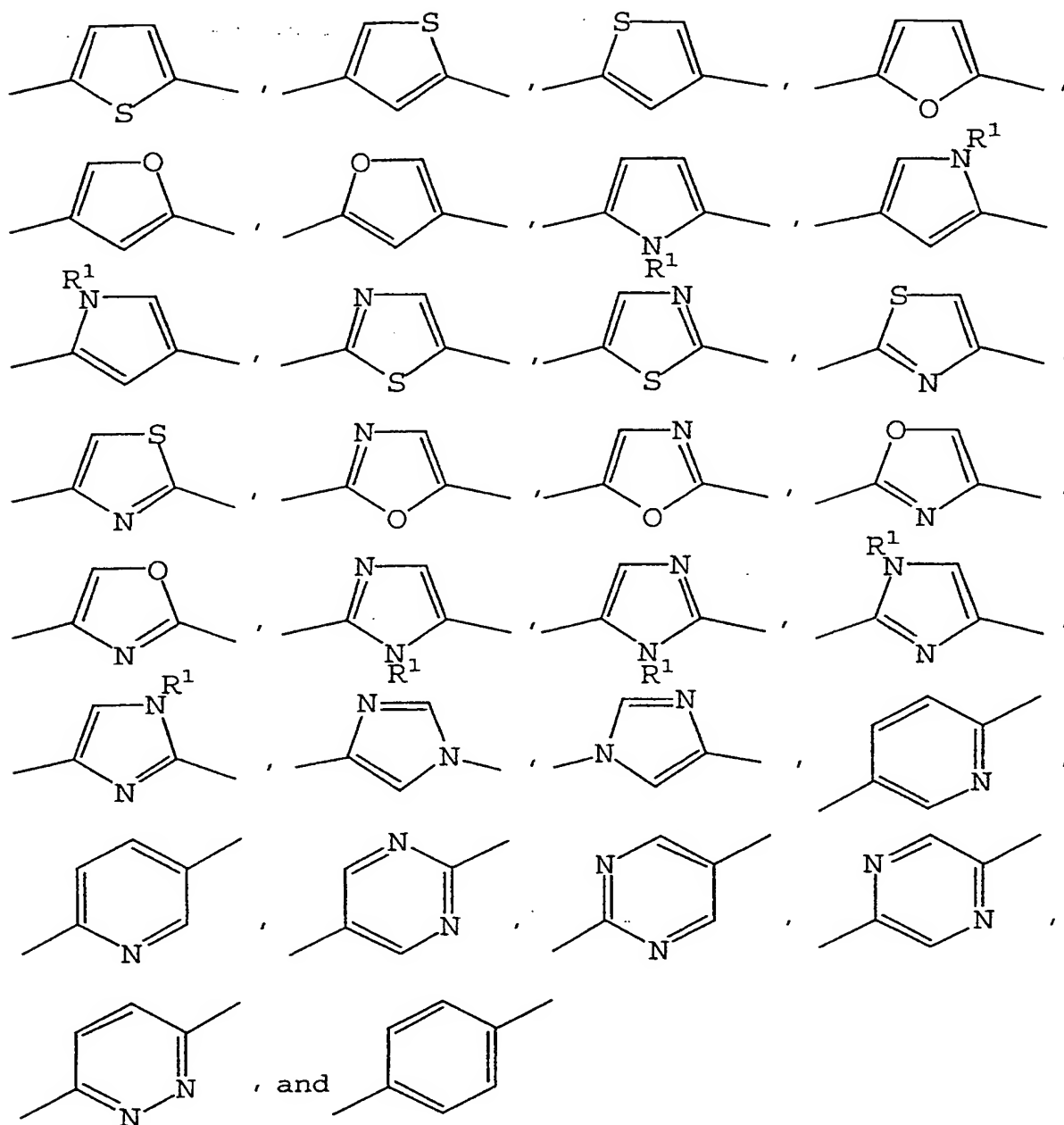
heterocycle, and b) unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

5

x is 0, 1, or 2;

10

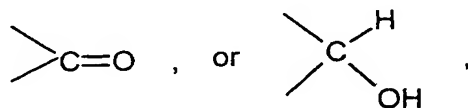
- (b) B represents a bond or an optionally substituted aromatic or hetero-aromatic ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a), the B rings being selected from the group consisting of:



wherein R^1 is as defined above and each R^1 may be the same or different:

5

(c) D represents



(d) E represents a chain of n carbon atoms bearing m substituents R^6 , wherein said R^6 groups are independent substituents, or constitute spiro or nonspiro rings in which a) two groups R^6 are joined, and taken together with the chain atom(s) to which said two R^6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R^6 is joined to the chain on which said one group R^6 resides, and taken together with the chain atom(s) to which said R^6 group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring; and wherein

n is 2 or 3;

m is an integer of 1 - 3;

each group R^6 is independently selected from the group consisting of:

* fluorine;

* hydroxyl, with the proviso that a single carbon may bear no more than one hydroxyl substituent

* alkyl of 1 - 10 carbons;

* aryl of 6 - 10 carbons;

* heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

* arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;

5

- * heteroaryl-alkyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;

- * alkenyl of 2 - 10 carbons;

- * aryl-alkenyl wherein the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;

10

- * heteroaryl-alkenyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 - 5 carbons;

- * alkynyl of 2 - 10 carbons;

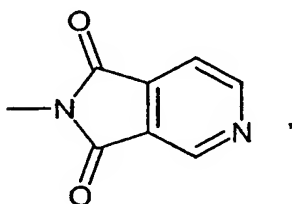
15

- * aryl-alkynyl wherein the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;

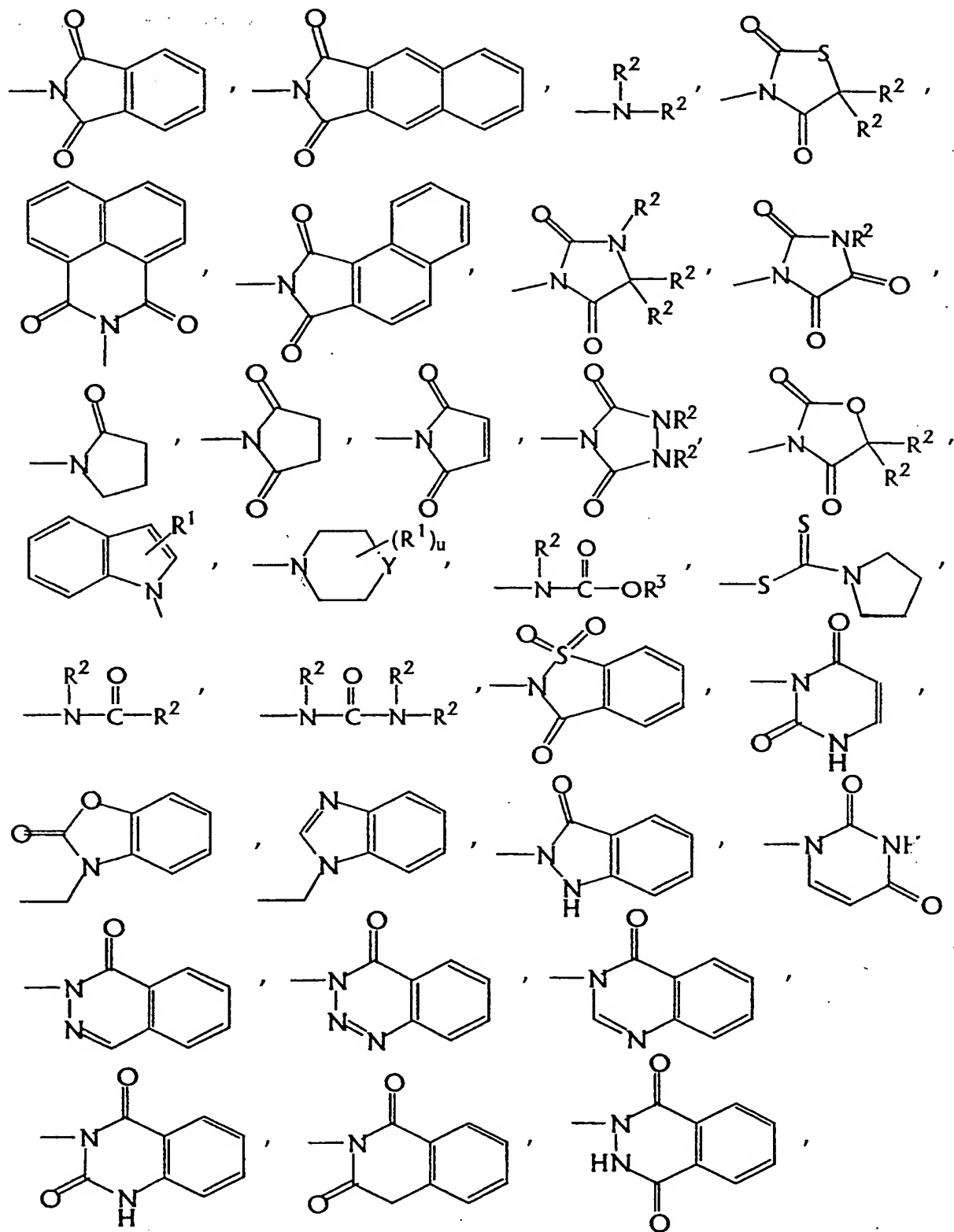
- * heteroaryl-alkynyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;

20

- * $-(CH_2)_tR^7$ wherein
t is 0 or an integer of 1 - 5; and
 R^7 is selected from the group consisting of



25



and corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R^7 group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

wherein

5

Y represents O or S;

R^1 , R^2 , and R^3 are as defined above and each R^1 , R^2 or R^3 may be the same or different; and

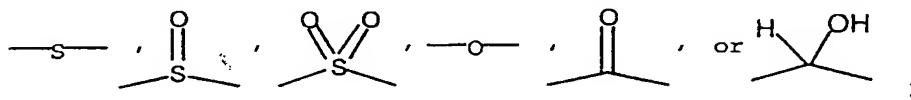
u is 0, 1, or 2; and

10

* $-(CH_2)_vZR^8$ wherein

v is 0 or an integer of 1 to 4; and

Z represents



15

R^8 is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

20

arylalkyl wherein the aryl portion contains 6 to 10 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

25

$-C(O)R^9$ wherein R^9 represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9

carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when R^8 is $-C(O)R^9$, Z is S or O;

5 - when Z is O, R^8 may also be $-(C_qH_{2q}O)_rR^5$ wherein q, r, and R^5 are as defined above; and

* $-(CH_2)_wSiR^{10}_3$ wherein

w is an integer of 1 to 3; and

10 R^{10} represents alkyl of 1 to 2 carbons;

and with the proviso that

15 - aryl or heteroaryl portions of any of said T or R^6 groups optionally may bear up to two substituents selected from the group consisting of $-(CH_2)_yC(R^4)(R^3)OH$, $-(CH_2)_yOR^4$, $-(CH_2)_ySR^4$, $-(CH_2)_yS(O)R^4$, $-(CH_2)_yS(O)_2R^4$, $-(CH_2)_ySO_2N(R^4)_2$, $-(CH_2)_yN(R^4)_2$, $-(CH_2)_yN(R^4)COR^3$, $-OC(R^4)_2O-$ in which both oxygen atoms are connected to the aryl ring, $-(CH_2)_yCOR^4$, $-(CH_2)_yCON(R^4)_2$, $-(CH_2)_yCO_2R^4$, $-(CH_2)_yOCOR^4$, -halogen, -CHO, -CF₃, -NO₂, -CN, and $-R^3$, wherein

20 y is 0 - 4; and

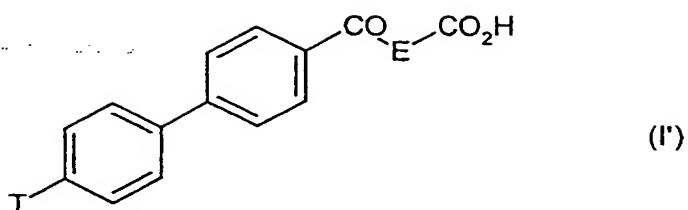
R^3 and R^4 are defined as above, and each R^3 or R^4 may be the same or different; and any two R^4 which are attached to one nitrogen may be joined to form a heterocycle;

25

and pharmaceutically acceptable salts and prodrugs thereof for the manufacturing of drugs for the treatment and prevention of multiple sclerosis.

2. Use according to claim 1 of compounds of the general formula (I')

30

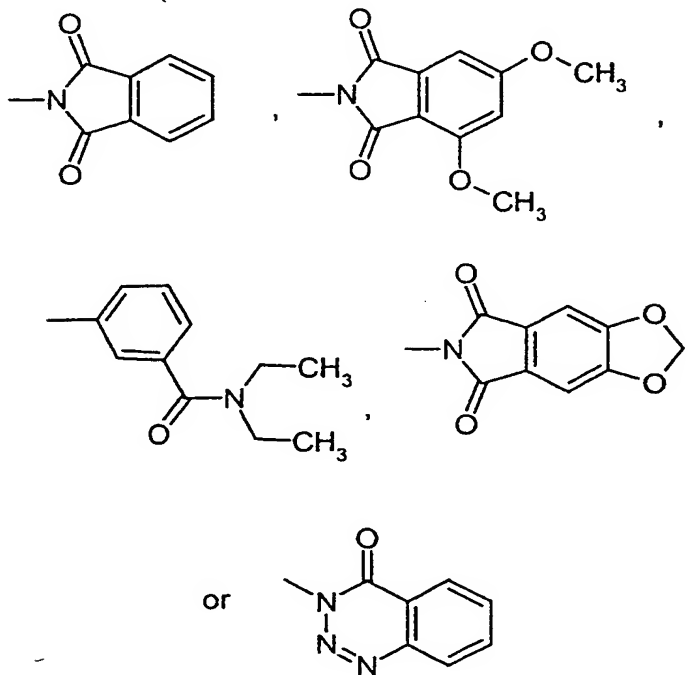


wherein

T is (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

CO-E-CO₂H represents a 3-carboxyl-5-(R⁷)-pentan-1-on-1-yl- or a [2-carboxyl-3-(R⁷)-methyl-cyclopentan-1-yl]-carbonyl-residue, wherein

R⁷ represents a group of the formula



and their salts.

3. Use according to claim 2, characterized in that the enantiomer of a pair of enantiomers at a chiral center adjacent to the carboxylic acid moiety of the

group of the formula CO-E-CO₂H in compounds of the general formula (I') more potently inhibits MMP-2 and/or MMP-9.

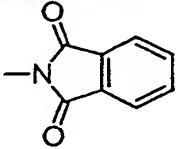
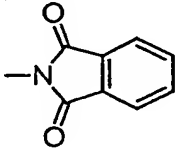
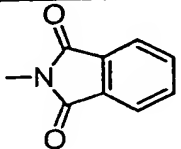
4. Use according to claim 1, wherein the compound is selected from the group consisting of

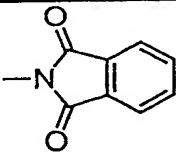
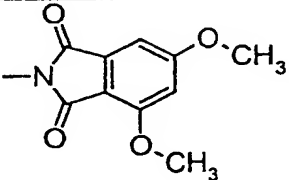
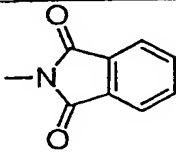
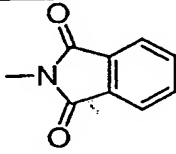
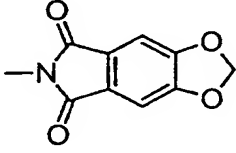
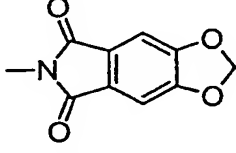
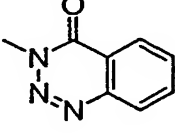
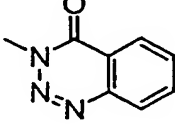
(+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxy[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,

(+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid,

or a salt thereof.

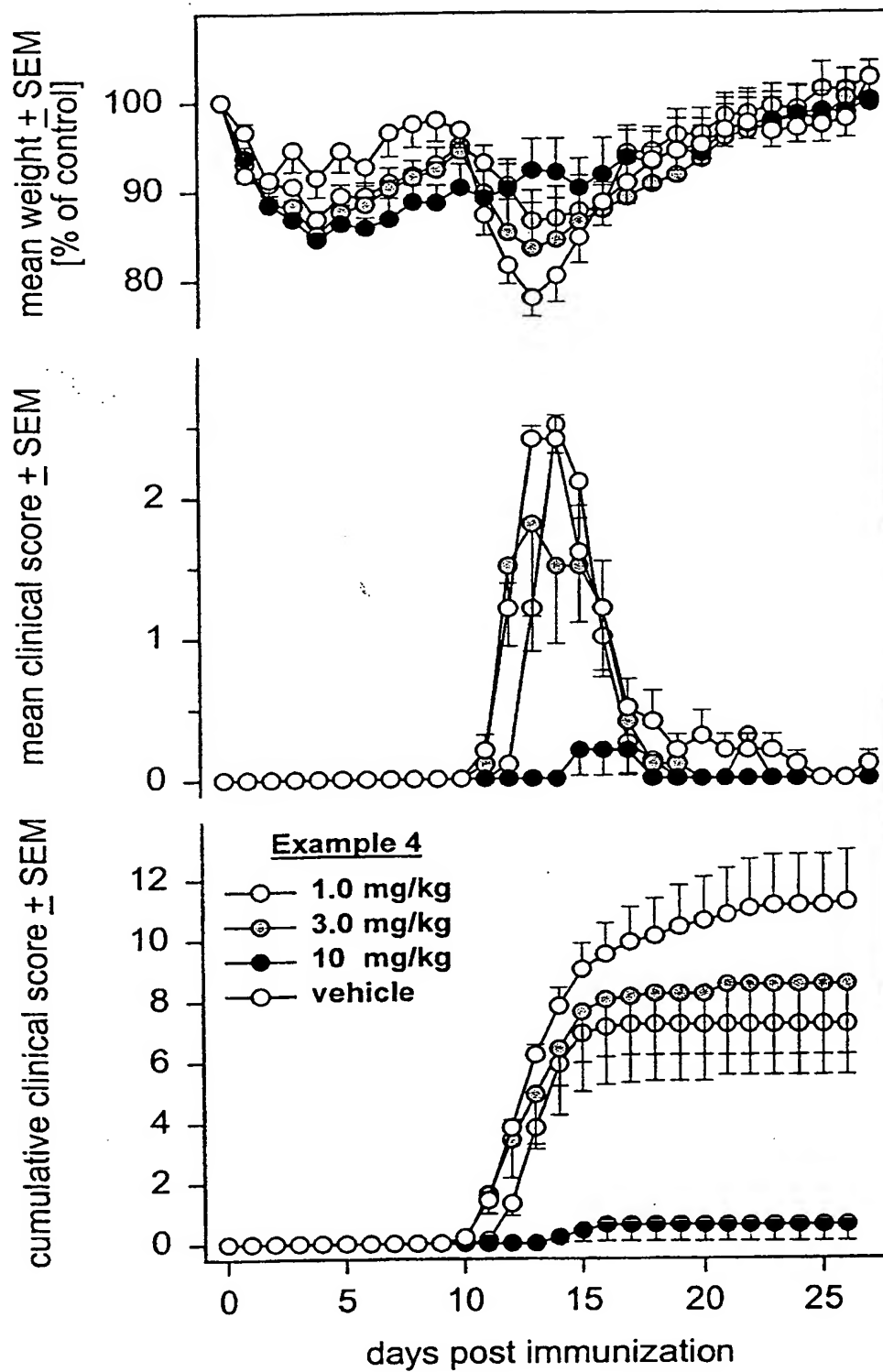
5. Compounds of the general formula (I'), wherein CO-E-CO₂H represents a 3-carboxyl-5-R⁷-pentan-1-on-1-yl-residue, and wherein T and R⁷ have the meaning indicated in the following table:

T	R ⁷	racemate, (+)- or (-)-enantiomer	
OEt		(+)	;
OEt		(-)	;
OAc		rac	;

T	R ⁷	racemate, (+)- or (-)-enantiomer	
OH		rac	;
Cl		rac	;
Br		(+)	;
Br		(-)	;
Cl		(+)	;
Cl		(-)	;
CN		rac	or
OCF ₃		rac	.

6. Pharmaceutical composition which as active constituent contains at least one compound according to claim 5 mixed together with at least one pharmaceutically tolerable essentially non-toxic vehicle or excipient.
- 5 7. Process for the preparation of a pharmaceutical composition according to claim 6.
8. Compound according to claim 5 for use as a medicament in the treatment of humans or animals.

Figure 1



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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LEA33914-W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/08890	International filing date (day/month/year) 12/09/2000	(Earliest) Priority Date (day/month/year) 24/09/1999
Applicant BAYER AKTIENGESELLSCHAFT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/08890

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1

Present claim 1 relates to the use of an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for the use of only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the use of the compounds according to formula (I') (claim 2) and the compounds listed in claims 4 and 5, their preparation, compositions and therapeutic use.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08890

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4035 A61K31/53 C07D209/48 C07D253/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 61413 A (BAYER AG) 2 December 1999 (1999-12-02) page 2, line 34 - line 38 examples 15,16	2
X	WO 97 43239 A (BAYER CORPORATION, USA; VAN ZANDT, MICHAEL C.; BRITTELLI, DAVID R.; DIX) 20 November 1997 (1997-11-20)	2
Y	page 11, line 7,8 cpd XIX	3-8
Y	WO 96 15096 A (SCHNEIDER STEPHAN ; BENZ GUENTER H H H (DE); DIXON BRIAN RICHARD (U) 23 May 1996 (1996-05-23) examples 262,267-269,360,419	2-8
	--- -/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

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International Application No

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